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MUSCULAR DEFECTS IN THE VENTRICULAR SEPTUM

BY

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Received December 3, 1954

Although defects in the muscular part of the inter-ventricular septum have been recognized since the time of Galen, they are rare. Selzer (1954) states that 90 per cent of isolated ventricular septal defects and virtually all those occurring with other malformations of the heart are located in the membranous septum and he believes that muscular defects are of no clinical importance since they are usually small and decrease in size or close during systole. A similar opinion is held by Kaplan and Robinson (1954) who consider that there is a remarkable absence of symptoms with defects in the muscular portion of the inter-ventricular septum. Such congenital defects may, however, be associated with a dramatic clinical picture as in the case now reported.

Case Report

A married woman, aged 21 years, was admitted as an emergency with hæmoptysis. She had been short of breath on exertion since infancy and had suffered from coughs and colds every winter. Her parents had noticed that her lips became blue when she was breathless and for this reason had taken her at the age of five years for examination by one of us (J.W.B.) when, on the basis of a loud præcordial systolic murmur, a ventricular septal defect was diagnosed. From the age of six she had had recurrent nose bleeding and her breathlessness on exertion had become worse but she was not cyanosed other than on exertion. At the age of twenty years she had coughed up a little bright red blood and after five weeks of repeated small hæmoptyses had suddenly coughed up a pint of blood. A year later she had had further hæmoptyses and this had continued until five days before her admission when she had complained of a bubbling sensation in her chest and coughed up a further pint of blood. Three days after admission she had a further profuse hæmoptysis and died.

On admission she was a tall thin girl with pallor of the skin and mucous membranes. There were no petechiæ. The fingers were long and tapering but were not clubbed. There was no cyanosis at rest but on slight exertion her lips became blue. The radial pulse was regular at 120 a minute and of poor volume. The blood pressure in the arms was 120/80 mm. Hg, and both femoral pulses were palpable and equal. The apex beat was palpable in the sixth left intercostal space just beyond the mid-clavicular line and the character of the cardiac impulse indicated right ventricular hypertrophy. The second heart sound was palpable in the pulmonary area. A loud systolic murmur was present over the whole præcordium but was of maximum intensity in the fourth left intercostal space two inches to the left of the sternum. The second sound in the pulmonary area was abnormally loud and split. The electrocardiogram showed sinus rhythm, clockwise rotation of a vertical heart, and a ventricular pattern of right ventricular hypertrophy (Fig. 1). On radiological examination there was moderate overall cardiac enlargement in the postero-anterior position and evidence of right ventricular hypertrophy in the left anterior oblique view. The pulmonary artery and its main branches were dilated and abnormally pulsatile but the degree of pulsation did not amount to a hilar dance: the vascularity of the lung fields was increased (Fig. 2). There was no evidence of pulmonary tuberculosis and no tubercle bacilli were found in the sputum. The hæmoglobin was 10·2 g. per 100 ml. Clinically the diagnosis was considered to be a ventricular septal defect with pulmonary hypertension.

* Leverhulme Research Scholar, Royal College of Physicians.

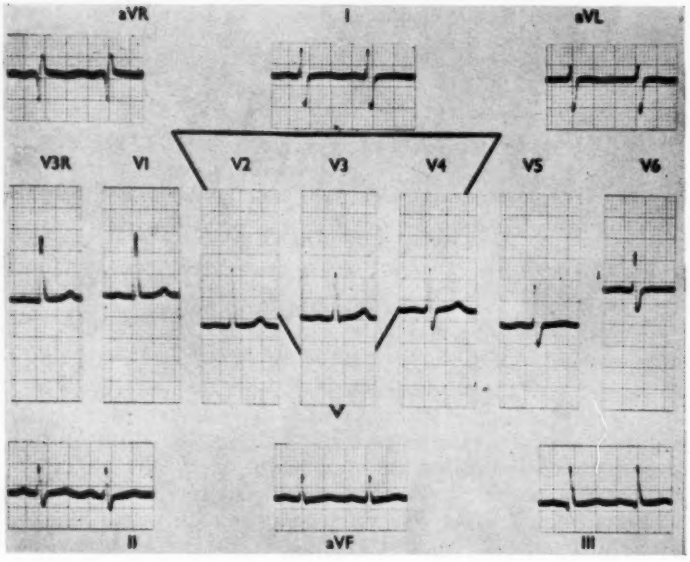

FIG. 1.—Electrocardiogram showing ventricular pattern of right ventricular hypertrophy and clockwise rotation of a vertical heart. 0·5 cm. equals 1 millivolt.

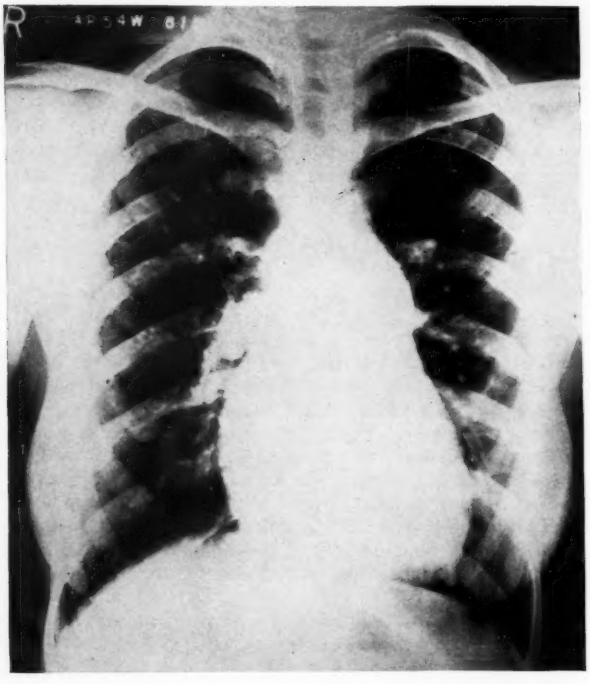

FIG. 2.—Postero-anterior teleradiogram of the chest showing moderate overall cardiac enlargement with prominence of the pulmonary artery and its main branches.

Necropsy Report

The heart was enlarged, mainly due to hypertrophy of the right ventricle (Fig. 3). The tricuspid valve was normal; there was no infundibular stenosis and the pulmonary valve was normal. The main pulmonary artery was dilated to twice its normal diameter and flecks of atheroma were present in the extrapulmonary portions. The left ventricle was not hypertrophied and the mitral valve had three cusps. There was a ventricular septal defect, 2 cm. in diameter, in the region of the apex (Fig. 4). This was traversed by one of the columnæ carneæ from the left ventricle and by one of the chordæ tendineæ of the mitral valve.

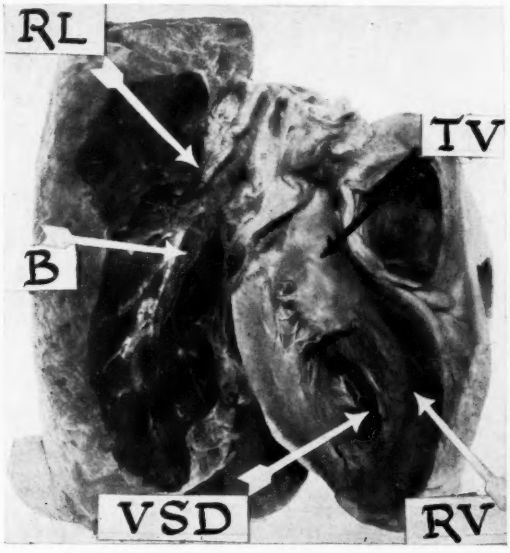

Fig. 3.—The heart and right lung dissected to show the muscular defect in the lower third of the ventricular septum. The right ventricle is hypertrophied. The bronchial tree contains antemortem clot. VSD=Ventricular septal defect. RL=Right lung. TV=Tricuspid valve. RV=Right ventricle. B=Bronchus.

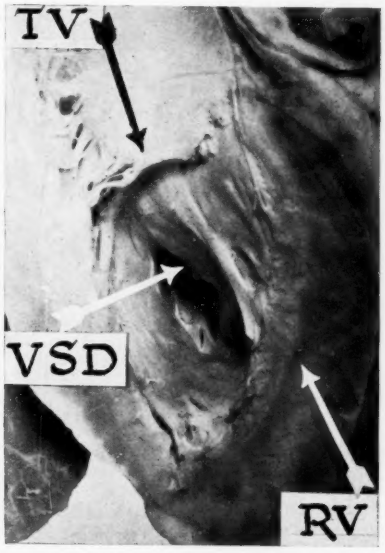

Fig. 4.—Close up view of the muscular defect which is crossed by one of the columnæ carneæ of the left ventricle. There is right ventricular hypertrophy. VSD=Ventricular septal defect. RV=Right ventricle. TV=Tricuspid valve.

There was no defect in the membranous part of the ventricular septum. The ductus arteriosus was not patent and there was no atrial septal defect. The upper lobe of the left lung was solid to the touch and the left upper lobe bronchus was blocked by blood clot (Fig. 3). The stomach was dilated and contained two pints of altered blood.

On histological examination there was no evidence of medio-necrosis of the extrapulmonary elastic arteries. Although atheroma had been noted in the extrapulmonary arteries it was not seen in the intrapulmonary portions. The muscular pulmonary arteries (100μ to 1000μ) showed severe and widespread changes and it was impossible to find a single muscular artery that could be passed as normal (Fig. 5, 6, and 7). The adventitia was thick and fibrous and was infiltrated in many cases by thin wisps of elastic tissue which had split away from the grossly thickened external elastic lamina. The media was hypertrophied with an abnormally thick layer of densely staining, circularly arranged, smooth muscle cells peripheral to the internal elastic lamina. This lamina was very thick and there were fine wisps of elastic tissue spreading into the media. The majority of the muscular arteries were occluded by young fibrous tissue or fibro-elastic tissue which had recanalized in many. Some arteries showed medial aplasia, the external and internal membranes fusing into a single lamina between proliferated intimal tissue and adventitia (Fig. 8). In some cases the media was absent for as much as 40 per cent of the circumference of the vessel and this was particularly in evidence in

FIG. 5.—Transverse section of muscular pulmonary artery. The media is hypertrophied and both elastic lamina are thick. There is proliferation of fibro-elastic tissue from the intima obliterating the lumen (Stain, Verhoeff/Van Gieson, ×144).

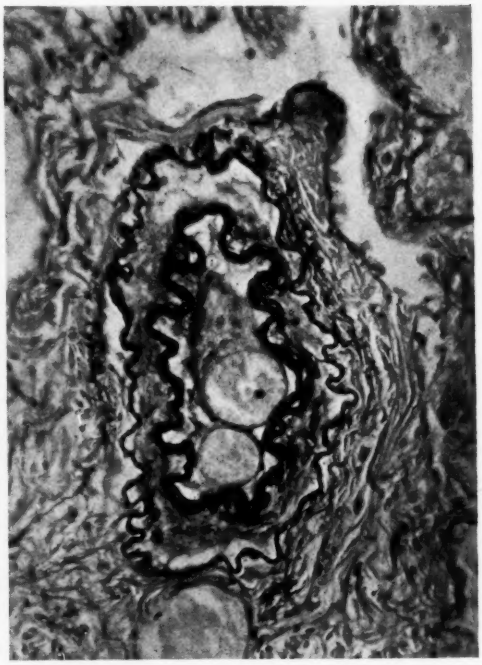

FIG. 6.—Transverse section of muscular pulmonary artery. Recanalization has occurred in the lumen of the vessel blocked by fibro-elastic tissue proliferated from the intima. The internal elastic membrane is very thick (Stain, Verhoeff/Van Gieson, ×290).

the region where the bronchioles opened into the infundibulum. At this site certain of the muscular pulmonary arteries appeared to communicate with vessels whose diameter was greater than that of the parent artery. These vessels, which were lined by fibro-elastic tissue and filled with blood, were at first thought to be aneurysmal sacs, since communications between artery and vessel were frequently seen. The external elastic lamina was thin in some places and in others had broken (Fig. 9). These appearances were different from normal branching of the pulmonary artery where the media and lamina are intact at all other places than that of emergence of the branch the diameter of which is considerably less than that of the parent vessel. However, on examination of serial sections these sacs were found to be grossly dilated branches of the parent vessel. The arterioles (less than 100μ) had a thick adventitia and a definite media bounded by distinct internal and external elastic membranes. Brenner (1935) pointed out that the normal arteriole consists of an endothelium lying on a single elastic lamina with no media. The veins showed crescents of sclerotic tissue, partially occluding the lumen.

DISCUSSION

The symptoms of breathlessness and cyanosis on exertion, frequent coughs and colds, and recurrent hæmoptysis, which occurred in the present case, are similar to those observed in patients with Eisenmenger's complex by Brown *et al.* (1955) and in other patients with patent ductus arteriosus complicated by pulmonary hypertension by Whitaker *et al.* (1955); they were considered by these authors to be characteristic of congenital heart disease complicated by severe pulmonary hypertension. There was clinical evidence of pulmonary hypertension in the present patient and cyanosis on

FIG. 7.—Transverse section of the muscular pulmonary artery. The elastic membranes are thick and there is elastic tissue in the media and adventitia. The lumen of the vessel has been obliterated by fibro-elastic tissue. Recanalization has occurred. A branch is emerging from the parent vessel (Stain, Verhoeff/Van Gieson, ×210).

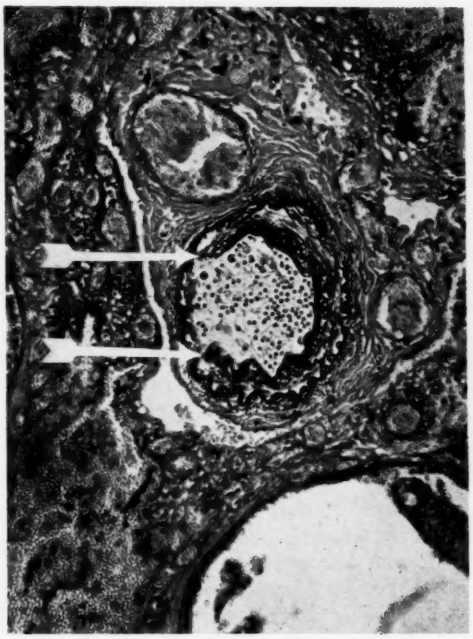

FIG. 8.—Transverse section of a muscular pulmonary artery. Aplasia of the media is seen between the points indicated by arrows. At these points the internal and external elastic laminæ fuse to form a single lamina seperating the adventitia and the proliferated fibrous tissue occluding the lumen of the vessel (Stain, Verhoeff/Van Gieson, ×122).

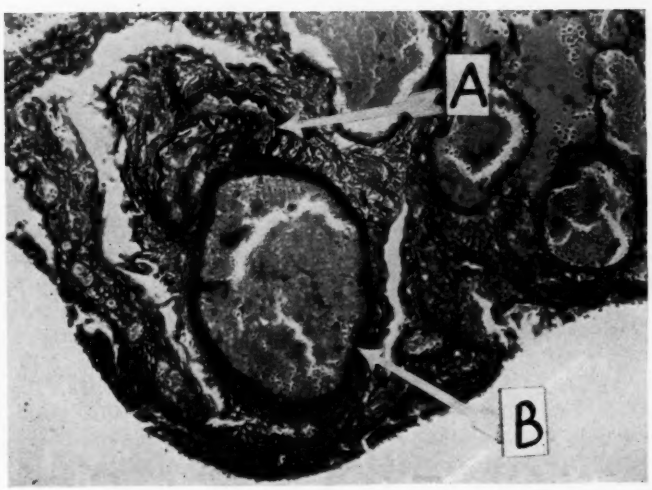

FIG. 9.—Transverse section of a muscular pulmonary artery. A blood filled sac (B) is seen in communication with the artery (A). This sac proved on serial section to be a grossly dilated branch of the parent vessel. The external elastic lamina has ruptured opposite the emergence of the dilated brach (Stain, Verhoeff/Van Gieson, ×122).

exertion, indicating that, as in some cases of defects of the membranous septum, a muscular defect of the interventricular septum may be complicated by pulmonary hypertension, right ventricular hypertrophy, and reversal of flow through the defect. Such complications were probably present in the case of Weiss (1927), where there was severe central cyanosis and in that of Konar and Sen Gupta (1954), where it was noted that the second pulmonary sound was loud and split and there was moderate cyanosis. Another patient with a muscular defect seen by one of us (J.W.B.) also had clinical signs of pulmonary hypertension. This boy had suffered from breathlessness on exertion and frequent chest infections, and died at the age of seven years from bronchopneumonia which was accompanied by central cyanosis but not congestive heart failure.

A harsh systolic murmur such as one heard in the present case has been present in all the reported cases (Weiss, 1927; Konar and Sen Gupta, 1954; Hemsath *et al.*, 1936; Edwards *et al.*, 1954; Kaplan and Robinson, 1954), and in the case of the boy mentioned above but there is no evidence that the maximum site of this murmur and its distribution allows it to be distinguished from the murmur of a septal defect in the membranous part of the inter-ventricular septum and the differentiation of these two conditions will probably only be made at necropsy.

Right ventricular hypertrophy appears to be a common feature of the anomaly. There was cardiographic evidence of right ventricular hypertrophy in the present case (Fig. 1) and also in the patients reported by Weiss (1927) and Konar and Sen Gupta (1954), which are the only previously reported patients where an account is given of the cardiographic findings. On radiological examination, there was right ventricular hypertrophy in the present patient and in that reported by Konar and Sen Gupta (1954). There was also cardiographic and radiological evidence of right ventricular hypertrophy in one patient previously seen by one of us.

Muscular defects may occur in the inter-ventricular septum in the region of the apex or midway between apex and membranous septum. In the case described by Konar and Sen Gupta (1954) the defect was in the apical region while in the case of Weiss (1927) it was midway between apex and mitral valve, and in the present patient it was in the lower third of the muscular septum. Brown and Gerlis (1954) have demonstrated two examples of ventricular septal defects that occurred in the central area of the muscular septum and were associated with dilatation of the main pulmonary artery and right ventricular hypertrophy, suggesting that pulmonary hypertension was present in life. Hemsath *et al.* (1936) reported the co-existence of muscular and membranous defects. Wimsatt and Lewis (1948) considered that defects of the ventricular septum are produced by aneurysmal dilatation of sinusoidal communications which occur in the septum developing between right and left ventricles as described in the pig embryo up to the 45-mm. stage by Bennett (1936). Examples of muscular defects in the ventricular septum have been described in animals. Olafson (1939) found in a calf an oblique defect similar to that described in a human being by Weiss (1927) and Wimsatt and Lewis (1948) described a large apical septal defect in a yak.

In addition to having a ventricular septal defect in an unusual site the present case is of interest for the histological appearances in the pulmonary arteries which have not previously been described in patients with muscular defects. Adventitial fibrosis, medial hypertrophy, and subintimal proliferation with eventual obliteration of the lumen by fibrous or fibro-elastic tissue showing recanalization occur in pulmonary arteries of patients with congenital heart disease complicated by severe pulmonary hypertension. Medial aplasia has been reported in the muscular pulmonary arteries in other forms of cardiac disease associated with pulmonary hypertension by Evans (1951) who believes that the combination of defective arterial wall and pulmonary hypertension lead to endarteritis fibrosa producing arterial obstruction and increasing the pulmonary hypertension. The unique feature in this case is the dilatation of the branches of the muscular pulmonary arteries occurring at the same site as medial aplasia. The recurrent hæmoptyses in the terminal phase of the patient's life were probably due to rupture of these vessels under the strain of pulmonary hypertension. Since hæmoptysis frequently occurs in patients with congenital heart disease complicated by severe pulmonary hypertension, the possibility that this is the result of rupture of dilated branches from pulmonary arteries should be borne in mind.

SUMMARY

A case of a muscular defect in the ventricular septum is described. The patient presented in life the picture of cyanotic congenital heart disease with pulmonary hypertension and died following a severe hæmoptysis. In addition to the usual histological features associated with severe hypertension the pulmonary arteries showed the unique feature of aneurysmal dilated branches arising from the muscular arteries.

We wish to thank Mr. C. Lambourne for his invaluable help with the sections.

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THE Q–T INTERVAL IN RHEUMATIC HEART DISEASE

BY

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There are differences of opinion concerning the significance of the prolongation of electrical systole as a diagnostic sign of active rheumatic-heart disease. Taran and Szilagy (1947, 1951, 1952), Abrahams (1949), and Solomon and Zimmerman (1951) maintain that a prolonged electrical systole is a reliable criterion of activity in rheumatic heart disease; Taran even considers that there is a close correlation between the length of $Q–T_c$ prolongation and the degree of carditis. Weinstein *et al.* (1950), Pokress and Goldberger (1949), as well as Gittleman *et al.* (1951) have reported that Q–T prolongation frequently occurs in active rheumatic fever, though they have not observed it in all cases. Craige *et al.* (1950) and Epstein (1950) do not agree with these views and find that even in severe carditis the Q–T interval does not exceed the upper limit of the normal.

This diversity of opinion has induced us to examine cases of rheumatic heart disease with a view to evaluating the significance of Q–T prolongation as indicating rheumatic activity and, at the same time, to determine the presence and frequency of other electrocardiographic abnormalities in active rheumatic fever. Moreover, we have included in our report a list of some of the patients operated on for mitral stenosis in whom histological examination of the auricular appendage supplied objective evidence of the presence or absence of carditis.

METHODS

From 157 subjects 164 electrocardiograms were obtained and examined. They were all recorded on a Cambridge string galvanometer, with the patients in the recumbent position. Only technically clear records were used.

Our cases have been divided into five groups.

Group I. 33 normal subjects who served as a control group—11 men, 11 women, and 11 children.

Group II. 56 electrocardiograms of 50 patients with rheumatic fever—12 men, 21 women, 17 children. The presence of activity was proved by clinical criteria (articular pains and swelling, and fever) and laboratory findings (increased sedimentation rate and leucocytosis). This group includes patients ranging in age from 4 to 52 years.

Group III. 31 electrocardiograms of 30 patients with "subclinical" rheumatic activity—5 men, 23 women, and 2 children. These patients had mild to moderate pains in the joints, a subfebrile temperature, and a heart murmur, but the laboratory examinations were normal.

Group IV. 30 patients with quiescent rheumatic heart disease—11 men, 16 women, and 3 children. These patients showed definite evidence of rheumatic valvular disease without great cardiac enlargement. There was no clinical or laboratory evidence of rheumatic activity.

Group V. 14 cases of mitral stenosis that underwent surgical treatment. In this group a histological examination of the auricular appendage was made.

Patients showing congestive heart failure, marked myocardial hypertrophy (Dreyfuss and Diengott, 1951), and those receiving digitalis or quinidine were excluded because of the well-known influence of these factors on the Q–T interval (Eden, 1951). Electrocardiograms showing auricular fibrillation and widening of QRS complexes were also excluded because of the unreliability of measurements in such cases.

* This study was supported by a grant from the Lown Fund.

The electrocardiograms were analysed for heart rate, P–R interval, S–T deviation, T changes, and the Q–T duration (electrical systole). The Q–T interval was measured in the customary manner from the beginning of the descent of the Q wave to the end of the T wave or, in the absence of a Q wave, from the ascent of the R wave, often with the aid of a lens.

The measured Q–T interval was then corrected for the cardiac rate, using the Taran and Szilagyi modification of Bazett's formula,

$$Q\text{–}T_{c\ (corrected)} = \frac{Q\text{–}T\ (measured)}{\sqrt{R\text{–}R\ (cycle\ length)}}$$

The measurements were made in three standard leads and in V1, V2, V5, five cycles being measured in each lead, i.e. 30 cycles altogether; then the average was calculated. In cases with tachycardia (over 100 a minute) or when much sinus arrhythmia was present, 6–8 cycles were measured in each lead.

The results obtained in the various groups were then submitted to statistical analysis.

RESULTS

Group I. Control cases. The common upper limit of the normal $Q\text{–}T_c$ in our material was found to be 0·412. Values above this figure were considered to be abnormal.

Group II. Patients with rheumatic fever (active rheumatic heart disease). Out of the 56 electrocardiograms 50 showed a $Q\text{–}T_c$ prolongation, i.e. a $Q\text{–}T_c$ interval longer than 0·412. The ranges were 0·414 to 0·528, the mean value 0·435. In six instances the electrocardiograms were repeated at least four months after the first recordings, while signs of rheumatic activity were still present; the $Q\text{–}T_c$ was found to be still prolonged.

Group III. Patients with " subclinical " rheumatic activity. Out of the 31 electrocardiograms 28 showed a $Q\text{–}T_c$ prolongation ranging between 0·415 and 0·468, with a mean of 0·433.

Group IV. Patients with quiescent rheumatic heart disease (non-active rheumatic heart disease). Out of the 30 records 28 showed a $Q\text{–}T_c$ below the upper limit of normal (less than 0·412), that is in this group a $Q\text{–}T_c$ prolongation was found in two cases only.

Group V. An attempt was made to compare the $Q\text{–}T_c$ values with the results of the histological examination of auricular appendages removed at the operation of mitral stenosis. Out of 10 cases with marked $Q\text{–}T_c$ prolongation two showed histological proof of rheumatic activity (Aschoff bodies); and two showed cellular accumulations closely resembling Aschoff bodies. In 4 cases with normal $Q\text{–}T_c$ interval no histological signs of any active rheumatic process could be traced.

Table I summarizes the results arrived at with regard to $Q\text{–}T_c$ prolongation in group II, III, and IV.

TABLE I

$Q\text{–}T_c$ IN ACTIVE AND QUIESCENT RHEUMATIC HEART DISEASE

	$Q\text{–}T_c$ prolonged		$Q\text{–}T_c$ normal	
	No. of cases	%	No. of cases	%
Group II	50	89	6	11
Group III	28	90	3	10
Group IV	2	7	28	93

A comparison of the frequency of occurrence of other electrocardiographic abnormalities with the incidence of $Q\text{–}T_c$ prolongation in groups II, III, and IV is best shown in the graphic representation of Fig. 1. The P–R interval was considered to be prolonged if it was longer than 0·20 in adults and 0·16 in children.

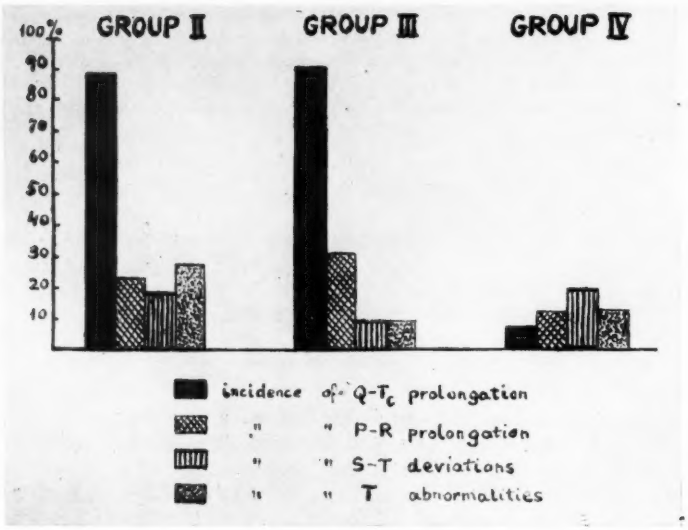

FIG. 1

STATISTICAL RESULTS (Group II and III)

(1) The results are highly significant in the sense that the lower limit of confidence is far above the upper limit of normal Q–T_c values (at any level of probability one may choose).

(2) The results in both groups (II, III) are similar, both in mean value and in dispersion.

(3) The distribution of Q–T_c values is unimodal, fairly symmetrical in group II and, in both groups (II, III), not significantly different from a normal distribution.

(4) The characteristic values are as follows:

	Group II	*Group III*
Average	0·4354	0·4332
Standard deviation	0·0269	0·0174
Standard deviation of average	0·0036	0·0031
The lower limit of confidence at P=0·0015 ..	0·4246	0·4239

(5) The following table gives an approximate idea of the gain in efficiency resulting from the use of the Q–T_c method alone, or in conjunction with other electrocardiographic abnormalities:

TABLE II

VALUE OF Q–T_c ALONE OR WITH OTHER CARDIOGRAPHIC ABNORMALITIES

	Group II		Group III	
Cases with:	Q–T_c prolonged	Q–T_c normal	Q–T_c prolonged	Q–T_c normal
P–R prolonged	11	2	10	0
P–R normal	39	4	18	3
S–T deviated	9	2	3	0
S–T isoelectric	41	4	25	3
T changed	16	0	3	0
T normal	34	6	25	3

Comment

The observations submitted in this paper were made with a view to evaluating the significance of a prolonged electrical systole (Q–T interval) in rheumatic heart disease. The Taran method was used for the calculation of the $Q–T_c$. Since it has been shown that changes in Q–T duration—if they exist—need not occur in every cardiac cycle (Taran and Szilagyi, 1952), a greater number of cycles must be measured and the average calculated before arriving at conclusions. For this we found 30 cycles sufficient and for higher cardiac rates 36–48 cycles.

As in every study dealing with Q–T measurements observation of normal cases proved of great importance. Our control subjects (group I) were of the same age group and lived in the same environment as did our patients; the children (from 4–14 years) had an upper limit of $Q–T_c$ 0·411; the women, 0·412; the men, 0·406. These results give a fair medial of the figures reported by other authors (Bazett, 1920; Abrahams, 1949; Epstein, 1950; Alimurung *et al.*, 1950; Yu *et al.*, 1951; and Taran and Szilagyi, 1947).

The results in group II indicate a significant prolongation of the $Q–T_c$ in about 90 per cent of the patients with active rheumatic heart disease. They confirm the reports of Taran and other authors, but do not agree with those of Pokress and Goldberger, who out of 50 patients with active rheumatic fever found a $Q–T_c$ prolongation in 14 only; our results also differ from those of Craige *et al.* (1950) who found normal Q–T intervals in 29 patients with fatal pancarditis; however, these authors did not state whether their patients had suffered from pericarditis, which has a marked shortening effect on the electrical systole (Taran and Ordorico, 1950).

The results obtained in group III proved to be of great importance for the clinical evaluation of the patients' condition. This group included a number of patients in whom such indications as subfebrile temperature, mild pains in the joints, and a heart murmur, together with a rheumatic past history, suggested active rheumatic carditis, though all the routine laboratory examinations gave normal results. It is evident that the significant $Q–T_c$ prolongation obtained in a large percentage of patients in this group makes the diagnosis of rheumatic activity possible. A comparative study was made between the frequency of occurrence of other electrocardiographic changes, such as P–R prolongation, S–T deviation, T wave abnormalities, and the $Q–T_c$ prolongation. The results obtained are very significant from the statistical point of view and prove that the $Q–T_c$ is a more sensitive diagnostic sign than the other electrocardiographic abnormalities known to occur in active rheumatic heart disease.

Our observations show that the active cases have a longer $Q–T_c$ than normal subjects and patients with quiescent (non-active) rheumatic heart disease. We have, therefore, come to the conclusion that the $Q–T_c$ prolongation may be considered as a diagnostic sign of active rheumatic heart disease.

Summary

One hundred and sixty-four electrocardiograms were examined for the Q–T interval, the P–R and S–T segments, and the T wave. The Q–T interval was corrected for cardiac rate and then the value submitted as the $Q–T_c$, according to the Taran modification of Bazett's formula.

Our investigation included five groups of cases: (1) normal control subjects, (2) patients with active rheumatic heart disease, (3) patients with rheumatic history suspected to be active, but without distinct evidence of activity (" subclinical activity "), (4) patients suffering from non-active (" quiescent ") rheumatic heart disease, and (5) a number of patients who underwent mitral valvotomy, which allowed a histological examination of the auricular appendage.

The common upper limit of the normal $Q–T_c$ was found to be 0·412.

In our groups (2) and (3) the $Q–T_c$ was found to be prolonged in about 90 per cent of cases and the statistical analysis showed the high significance of the obtained values. On the contrary, the $Q–T_c$ in patients with non-active rheumatic heart disease was found to be below the upper limit of normal in over 93 per cent of cases.

The frequency of occurrence of other electrocardiographic abnormalities in active cases was found to be far below the incidence of the Q–T_c prolongation.

We thus conclude that the Q–T_c prolongation may be used as a sensitive indicator of rheumatic activity.

We wish to thank Dr. A. Laufer, Pathologist, Hebrew University, Hadassah Medical School, for his advice and help in re-examining the histological findings in patients listed in group V, and Mr. E. Peritz, Statistician, for his aid in the statistical evaluation of our material. The mitral valvotomies were performed by Dr. H. Milwidsky.

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LEAD V4R IN RIGHT VENTRICULAR HYPERTROPHY

BY

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The cardiographic criteria generally used for the diagnosis of right ventricular hypertrophy are those proposed by Myers *et al.* (1948) following the work of Wilson *et al.* (1944). Experience of these criteria has shown that although they rarely give false positive results, many cases of right ventricular hypertrophy are missed. To meet this difficulty, Myers and his associates suggested the use of leads from positions further to the right of the sternum, and mentioned two instances in which a diagnosis of right ventricular hypertrophy was made from the appearance of V3R when the diagnostic pattern was absent from the remaining leads. Rosenman *et al.* (1950) also found V4R essential for the diagnosis of right ventricular hypertrophy in 5 of 25 cases but no systematic evaluation of this lead has been made.

In the present study the pattern of V4R has been examined in a control series of autopsies, in a series with pathological proof of right ventricular hypertrophy, and in a clinical series of adults with evidence of right ventricular hypertrophy. In addition we have compared the relative value of V4R, V1, and aVR.

Pathological Methods and Criteria. Assessment of the degree of ventricular hypertrophy at autopsy is difficult, but an attempt was made by taking the measurement of maximum thickness of the ventricle in the region of the outflow tract, and by employing the classification of Pagnoni and Goodwin (1952). Right ventricular thickness between 5 and 7 mm. was described as slight, 8–10 mm. as moderate, and 10 mm. or more as severe. Left ventricular thickness between 15 and 18 mm. was described as slight, 19–24 mm. as moderate, and 24 mm. or more as severe. Cases with cardiac infarction were excluded.

Cardiographic Methods and Criteria. V4R was recorded from the right chest anteriorly at the intersection of the mid-clavicular line with the fifth intercostal space. In all patients, the standard and unipolar limb leads, and V1, V2, V4, and V6 were recorded. In some instances V5R, V3R, V3, V5, and V7 were also obtained. The criteria used for the diagnosis of right ventricular hypertrophy were those of Myers *et al.* (1948).

The term incomplete right bundle-branch block has been avoided. Instead, the description rSr′ has been applied to QRS complexes of a duration of less than 0·12 sec. showing either secondary r′ wave smaller than the S wave, or an embryonic r′ wave notching the S wave; the term rSR′ has been applied to complexes in which the secondary R wave was greater than both the initial r wave and the s wave.

Material. The study is divided into three parts.

I. Controls. The electrocardiograms of 73 subjects in whom autopsy showed no right ventricular hypertrophy were studied. There were 25 cases of left ventricular hypertrophy ranging in degree from slight to severe, and in the remainder, no ventricular hypertrophy was present. The age of these cases ranged from 18 to 88 years.

II. Electrocardiograms were studied of 31 cases in which autopsy showed hypertrophy of the right ventricle alone, and in 52 cases in which hypertrophy of both ventricles was present.

* During the tenure of a World Health Organization Fellowship.

III. A series of a further 96 electrocardiograms showing abnormalities in V4R and/or in V1 was studied and comparison made of the frequency of occurrence of abnormalities of the two leads.

RESULTS

I. Controls. In 64 of the 73 autopsy cases in which the right ventricle was normal, V4R showed rS or QS patterns resembling those normally found in V1. The rSr′ pattern was found in 4 cases, rSR′ in one, and there was one example each of left and right bundle-branch block. In two instances a Q wave was present without evidence of infarction, and in both of these it seemed that an isoelectric beginning of the QRS may have caused complexes which were really rSr′s′ and rSR′ to simulate QRS and QR complexes respectively.

Throughout this control group the R wave was smaller than the S wave in V4R as well as in V1. It was therefore concluded that the pattern R>S in V4R could be tentatively regarded as diagnostic of right ventricular hypertrophy provided that children and patients with ischæmic heart disease were excluded.

On the other hand rSr′ complexes have been shown to occur commonly in right præcordial leads in normal subjects (Camerini and Davies, 1955), and although a secondary r′ wave tends to grow larger as right-sided hypertrophy develops (Mounsey *et al.*, 1952*a*), rSR′ complexes may nevertheless occur in its absence. One such case was found in this control group, in addition to one example of complete right bundle-branch block. These patterns can therefore be regarded only as suggestive signs, and in the succeeding parts of this study, only the pattern R>S in V4R or V1 has been regarded as diagnostic of right ventricular hypertrophy.

II. (*a*) *Lone Right Ventricular Hypertrophy.* Of the 31 cases with lone ventricular hypertrophy at autopsy, the R>S pattern was present in V4R in 11 and in V1 in only 4 of these. In the seven cases in which the R>S pattern was found only in V4R, V1 showed normal patterns in 5 and rSR′ complexes in two. Lead aVR showed a dominant R wave in four cases (Fig. 1).

The finding in the 20 cases in which neither V4R nor V1 were diagnostic were as follows:

Normal patterns were found in V4R in 11 cases; in V1 in 13 (Fig. 2)											
rSr′	,,	,,	,,	,,	,,	5	,,	;	,,	V1	,, 5
rSR′	,,	,,	,,	,,	,,	2	,,	;	,,	V1	,, none
Right bundle-branch block was seen					,,	1	,,	;	,,	V1	,, 1
Left	,,	,,	,,	,,	,, ,,	1	,,	;	,,	V1	,, 1

In these 20 cases, hypertrophy was slight in 12 and moderate in 6: in one of the two severe cases right bundle-branch block was present; in the other, both V4R and V1 were normal.

(*b*) *Combined Ventricular Hypertrophy.* The R>S pattern was found in V4R in 11 of the 52 patients (21%) and in V1 in only 6 of these (12%). In the other 5 cases in which V4R was diagnostic V1 showed normal patterns in 3 and rSr′ patterns in 2 (Fig. 3). Lead aVR showed a dominant R wave in 6 cases (Fig. 4).

The findings in the 41 cases in which neither V4R nor V1 were diagnostic of right ventricular hypertrophy were as follows.

Normal patterns were found in V4R in 32 cases; in V1 in 34 (Fig. 5)											
rSr′	,,	,,	,,	V4R	,,	5	,,	;	,,	V1	,, 3 (Fig. 6)
Right bundle-branch block				V4R	,,	4	,,	;	,,	V1	,, 4.

Of these 41 cases, 31 had moderate or severe left ventricular hypertrophy. Of the remaining 10 with slight left-sided hypertrophy, the right ventricular hypertrophy was slight in 6, and moderate in 4 cases.

III. The 96 patients whose electrocardiograms showed abnormalities in V4R and/or in V1 have been considered in three groups according to the pattern found: (i) 66 patients showed an R>S pattern, (ii) 20 patients showed an rSr′ complex, and (iii) 10 patients showed an rSR′ pattern.

(i). In this group only 27 patients showed a dominant R wave in aVR, and 28 an R>S in V1.

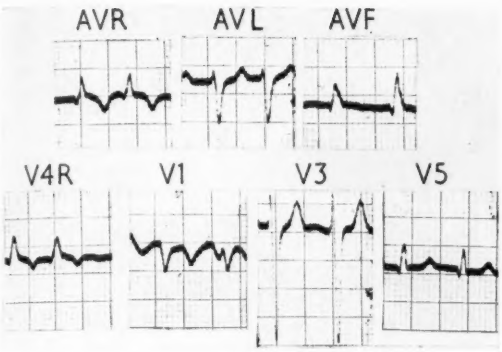

FIG. 1.—Cardiogram of patient with autopsy evidence of severe lone right ventricular hypertrophy. A dominant R wave is present in aVR and V4R but not in V1. Rhythm, auricular flutter.

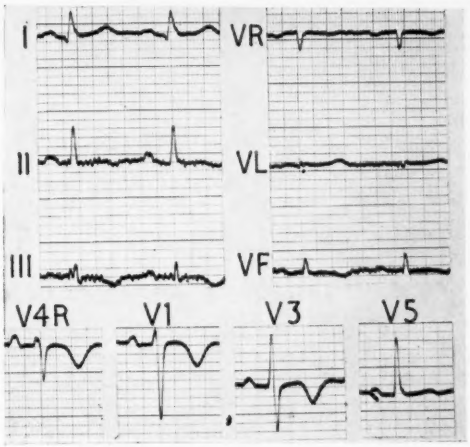

FIG. 2.—Cardiogram of patient with autopsy evidence of slight lone right ventricular hypertrophy. Leads V4R, V1, and aVR, show rS patterns. T wave inversion in V4R, V1, and V3 alone suggests right ventricular strain.

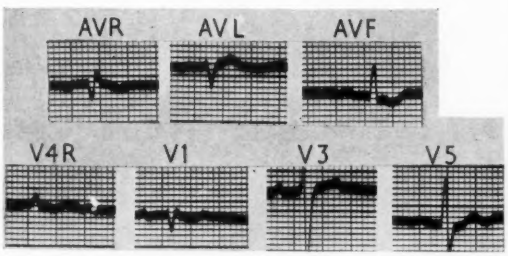

FIG. 3.—Cardiogram of patient with autopsy evidence of moderate hypertrophy of the right ventricle, and slight hypertrophy of the left ventricle. V4R shows a small R wave, while V1 shows rSr′. There is a Qr pattern in aVR.

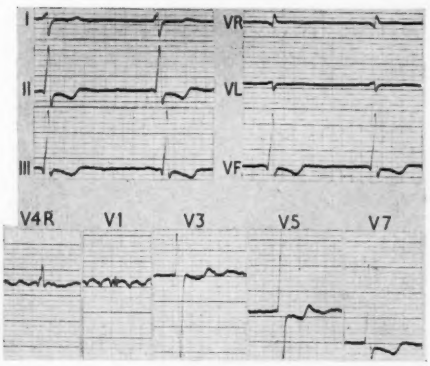

FIG. 4.—Cardiogram of patient with autopsy evidence of moderate right and left ventricular hypertrophy. V4R shows a dominant R wave and V1 an rSr′. aVR shows a qR pattern. Rhythm, auricular fibrillation.

Only one patient showed R>S in V1 when it was not present in V4R. By contrast, 38 patients showed R>S in V4R alone; in these cases V1 showed rS or QS in 17 (Fig. 7), rSr′ in 10 (Fig. 8), rSR′ in 8, and QRS patterns in 3. In these patients, the conclusive diagnosis of right ventricular hypertrophy depended on V4R alone, and in 30 of them, there was clinical or radiological evidence supporting this diagnosis: of the remainder, right ventricular hypertrophy might have been expected in 2, but was unexpected in 6 cases who presented no corroborative evidence of it. Of the 27 patients who showed R>S in both V4R and V1, 26 had supporting clinical and radiological evidence of right-sided hypertrophy, but in the remaining case the finding was unexpected.

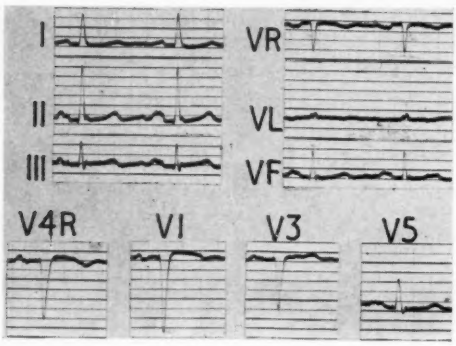

FIG. 5.—Cardiogram of patient with autopsy evidence of moderate hypertrophy of both ventricles. Leads V4R, V1 and aVR all show normal patterns: no evidence of left or right ventricular hypertrophy.

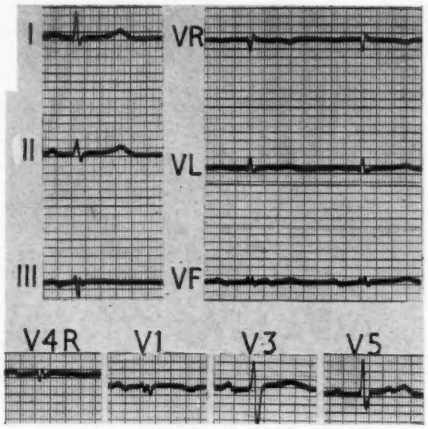

FIG. 6.—Cardiogram of patient with autopsy evidence of moderate right ventricular hypertrophy, and slight left ventricular hypertrophy. Leads V4R, V1, and aVR all show rsr′ patterns.

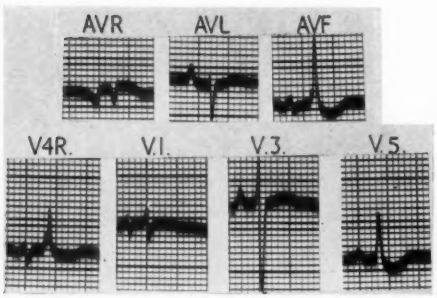

FIG. 7.—Cardiogram of patient with chronic cor pulmonale and clinical evidence of right ventricular hypertrophy. Lead V4R shows a dominant R wave and V1 an rS pattern. aVR shows a Qr complex. V4R is thus the sole sign of right ventricular hypertrophy.

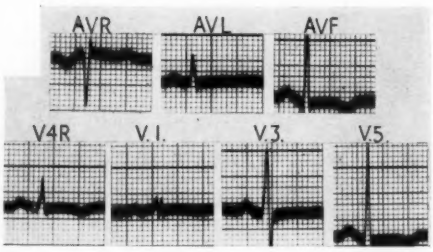

FIG. 8.—Cardiogram of patient with mitral stenosis and clinical evidence of right ventricular hypertrophy. V4R shows a dominant R wave, and aVR, and V1 rSr′ patterns.

(ii). Of the 20 patients in this group, 9 showed rSr′ patterns in V4R together with normal patterns in V1; the remainder showed rSr′ patterns in both leads. Four patients showed a dominant R wave in aVR. In two of the patients in whom rSr′ was present in V4R alone, and in two in whom it was present in both leads, the clinical evidence was not suggestive of right ventricular hypertrophy. In the remainder, the clinical findings were compatible with that diagnosis.

(iii). Of the 10 patients in whom V4R showed rSR′ complexes, aVR showed a dominant R wave in 1, V1 showed rSR′ patterns in 6, R>S in 1, and rSr′ in 3. In one of the last, the clinical findings were not suggestive of right ventricular hypertrophy; in the remainder they were suggestive or at least compatible with that diagnosis.

Discussion

It is probable that the pattern R>S in V4R in adult subjects is almost invariably diagnostic of right ventricular hypertrophy. In our autopsy series, confirmation of a diagnosis based on this sign was always obtained and the pattern was found most frequently among cases with marked hypertrophy. The diagnostic appearance was not seen in the control group in which right ventricular hypertrophy was absent. Cases of cardiac aneurysm and postero-lateral infarction must, however, be excluded from this generalization, for Levy *et al.* (1950) have shown that these conditions may produce a dominant R wave in V1 and we have also found it in V4R in such cases. Also the pattern may occur in V4R and V1 transiently in the course of acute or chronic bronchitis or temporary right ventricular strain (Fig. 9 and 10). The pulmonary artery pressure is known to be transiently raised in such circumstances (Mounsey *et al.* (1952*b*), but it seems unlikely that hypertrophy develops and disappears within a few days. The pattern in these cases, as indeed in those associated with hypertrophy, may be due to alteration in the position of the heart. This will be further discussed. There remain six cases in which an R>S pattern in V4R was the only sign of right ventricular hypertrophy of which there was no corroborative evidence elsewhere in the cardiogram or in the clinical findings. It would seem that in such circumstances caution must be exercised before undue significance is attached to a single cardiographic sign.

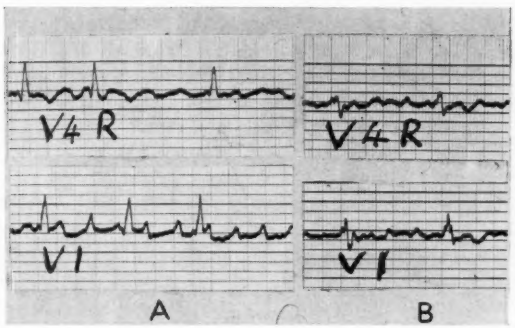

Fig. 9.—(A) Leads V4R and V1 from the cardiogram of a patient with mitral stenosis and auricular fibrillation taken during an episode of increased right ventricular stress. Both leads show unequivocally dominant R waves indicating right ventricular enlargement. (B) The same leads from the same patient after clinical improvement. There is now a definite S wave, and the R wave is smaller, suggesting less marked right ventricular stress, although there is some variation in the complexes from beat to beat.

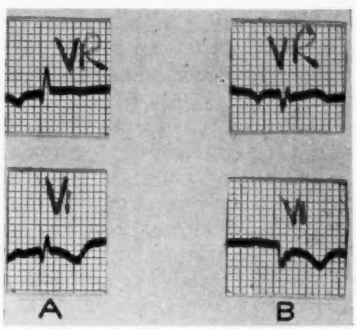

Fig. 10.—(A) Leads aVR and V1 from the cardiogram of a patient with cor pulmonale and an exacerbation of bronchitis. Both leads show dominant R waves indicating right ventricular enlargement. (B) The same leads from the same patient ten days later, after resolution of the acute attack. There is a predominantly negative deflection in both leads, suggesting resolution of the acute right ventricular stress.

The significance of rSR′ patterns is less clear cut. They may occur as a stage in the evolution of right bundle-branch block, which itself is not invariably associated with right ventricular hypertrophy. On the other hand they were not found in normal subjects by Camerini and Davies (1955), and occurred only once in our control series of autopsies without right ventricular hypertrophy. In the others in which this pattern was seen, right ventricular hypertrophy was proven at autopsy in 2, and was clinically suspect in 9, but probably absent in 1 case. It follows that this pattern is suggestive but not diagnostic of right ventricular hypertrophy. It was found in 12 cases in V4R and in 16 cases in V1. In 4 cases V4R showed R>S when V1 showed rSR′.

The rSr′ pattern occurs commonly in right præcordial leads in normal subjects (Camerini and

Davies, 1955). On the other hand, Mounsey *et al.* (1952*a*) have shown that an " embryonic " r' wave may appear and grow progressively larger as right ventricular hypertrophy develops in the course of pulmonary heart disease. It follows, therefore, that a single record showing this pattern is in no way diagnostic of right ventricular hypertrophy, but its appearance or progression is suggestive. In all cases in our series in which V1 showed this pattern, V4R showed either the same pattern or one more strongly suggestive of right ventricular hypertrophy.

The accuracy of the cardiographic diagnosis of right ventricular hypertrophy was considerably improved by the use of lead V4R which showed a diagnostic pattern in 27 per cent of autopsy-proved right ventricular cases, compared with 12 per cent in V1 and aVR. In the remaining cases suggestive rSr' and rSR' patterns were found as often in V4R as in V1. The frequency with which even V4R was diagnostic, was nevertheless low. This was partly accounted for by the inclusion of cases of combined ventricular hypertrophy. In the latter group, the greater the degree of left ventricular hypertrophy, the less frequently was the R>S pattern seen in V4R. In cases of lone right ventricular hypertrophy, V4R was diagnostic in 35 per cent and failures occurred most often in the cases with slight hypertrophy.

Taking the clinical and autopsy series together, there were 81 cases of proved or probable right ventricular hypertrophy in which R>S was seen in V4R and/or V1. In 44 (54%) it was found in V4R alone but in only one instance was it present in V1 alone, V4R showing rSR'.

The mode of production of the R>S pattern in V1 has been the subject of much controversy. Those workers who assume that præcordial lead patterns are derived predominantly from the activation of the muscle underlying the electrode have naturally supposed that qR or Rs patterns represented the specific pattern of the hypertrophic right ventricle. The presence of an initial negative deflection (Q wave) has been attributed by Myers (1950) to one of two factors: either abnormal activation of the septum or normal activation but with the production of so small an r wave that it is not transmitted to præcordial leads. Fowler *et al.* (1950) found that initial negativity in the right ventricular cavity could occur in subjects with right ventricular hypertrophy and thought that this was due to interference with the normal left-to-right septal depolarization. Possibly in some cases the initial small r waves due to normal septal activation are not recorded in V1 owing to spread of the impulse in a plane parallel with that of the lead. This would cause the beginning of the QRS interval to be iso-electric; the initial downward deflection, which by definition must be called Q, would be in reality an S wave and the final deflection would really be a secondary R wave. The whole complex would then be essentially an rSR' pattern, of which the final R' might represent activation of the right ventricle.

However, McGregor (1950) and Carouso *et al.* (1952) failed to find qR patterns in direct leads obtained from the right ventricular surface at operation, and McGregor (1950) and Sodi-Pallares *et al.* (1952) have suggested that such patterns are produced by rotation of the heart.

The assumption that præcordial lead patterns are derived predominantly from the muscle underlying the electrode has recently been subjected to much criticism by Scherlis *et al.* (1951), v. Luterotti (1951), Milnor *et al.* (1953), and Grishman *et al.* (1953). This assumption would appear to be wrongly based on the work of Wilson *et al.* (1944), who, although emphasizing the similarity between direct and præcordial leads, nevertheless stated . . . " that, although the excitation of the muscle in contact with the exploring electrode produces a much larger and much more sudden fluctuation in the potential of this electrode, than the excitation of any equal mass of muscle at a greater distance from it, every unit of ventricular muscle, without exception, produces action currents which contribute to the form of these complexes."

The results of our study strongly suggest that qR and Rs patterns are not predominantly derived from the potential variations of the right ventricle. The magnitude of potential variations recorded by a remote electrode varies inversely with the cube of its distance from the electrical source. It follows that the more remotely an electrode is placed from the heart, the more equally it is influenced by the potential variations of the two ventricles. If qR or Rs patterns were predominantly derived from the right ventricle they would be expected to be recorded most frequently and conspicuously

from the position closest to the right ventricle. In fact the reverse was found to be the case; V4R showed the qR and RS pattern more frequently and more conspicuously than V1. Since V4R is a remote lead and may be influenced fairly equally by the potential variations of all parts of the heart, it is probable that the abnormal R>S pattern displayed by it is a manifestation of the alteration in the direction of the vector loop in the horizontal plane, which has been shown to occur in right ventricular hypertrophy (Lasser *et al.*, 1951; Grishman and Scherlis, 1953; Shillingford and Brigden, 1954). This alteration is probably due to a combination of factors, including alteration of the relative position of the two ventricles, the relative magnitude of their electrical forces, and the direction of spread of the impulse. Altered direction of the horizontal vector loop may also account for qR and RS patterns in V1. It seems to us most unlikely that V1 can ever be regarded as a semi-direct lead from the right ventricle. In normal subjects the fourth intercostal space at the right sternal border overlies the right atrium (Gray's Anatomy, 1954), and cardiac catheterization has shown that the tricuspid valve is a mid-line structure and may be displaced to the left in right ventricular hypertrophy. It follows that both in normal subjects and cases of right-sided hypertrophy, lead V1 overlies the right atrium and records the sum of the potential variations of that chamber together with those of the rest of the heart. There would therefore appear to be no grounds for the widespread assumption that qR and RS patterns recorded from V1 represent the potential variations of the epicardial surface of the right ventricle.

The view that both V4R and V1 should be regarded as remote leads, is supported by the fact that aVR, which cannot be supposed to be dominated by right ventricular potentials, frequently shows qR or RS patterns resembling those found in the same case in V4R and V1, and such patterns have been shown to be reliable evidence of right ventricular hypertrophy (Goodwin, 1952).

Summary

The cardiograms of 252 adult subjects were studied with special reference to leads V4R, V1, and aVR. Cases of ischæmic heart disease were excluded. An rS pattern was the usual finding in V4R and V1 in a control series of 73 cases with no autopsy evidence of right ventricular hypertrophy. Although an rsr′ occurred twice, and an rSR′ once, an Rs pattern was not seen.

Eleven of 31 cases with autopsy evidence of right ventricular hypertrophy showed a dominant R wave diagnostic of this in V4R, but it was present also in V1 in only 4. Normal rS, rsr′, or rSR′ patterns occurred in the others. In a series of 52 cases with autopsy evidence of combined ventricular hypertrophy, the Rs pattern was present in V4R in only 11, and in V1 in 6 of these.

The cardiograms of 96 patients with clinical evidence suggesting right ventricular hypertrophy were also examined: 66 patients showed an Rs pattern in V4R, but less than half of these also had this pattern in V1 or aVR. Only one had an Rs pattern in V1, when it was not present in V4R.

The results indicate that V4R is a valuable lead in the diagnosis of right ventricular hypertrophy, often presenting a diagnostic Rs pattern in cases in which this is not present in V1 or aVR. Despite this, a proportion of cases remains in which V4R is normal. The Rs pattern was seen in V4R most frequently in subjects with considerable, rather than slight, right ventricular hypertrophy.

It is concluded that an rSr′ pattern in V4R or V1 alone is not diagnostic of right ventricular hypertrophy, while an rSR′ is suggestive, but not diagnostic. The genesis of the diagnostic Rs pattern in V4R and V1 is discussed, and it is suggested that these are remote rather than semi-direct leads.

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PARADOXICAL SPLITTING OF THE SECOND HEART SOUND

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The second heart sound is caused by closure of the aortic and pulmonary valves at the end of ventricular systole. Two components, from the separate closure of the two valves, are usually audible because of slight asynchrony of the two ventricles, aortic closure preceding pulmonary closure in normal subjects (Leatham and Towers, 1951). Potain (1866) observed that the character of the second heart sound altered with respiration. While it might be single during the expiratory phase of continued respiration it became clearly split with inspiration. Such a change in the second sound is found in most normal subjects and is due to prolongation of right ventricular systole during inspiration. This may be explained by the increased filling of the right atrium and ventricle from the great veins which takes place with the inspiratory fall in intra-thoracic pressure. No such change can occur on the left side of the heart since intrathoracic pressure changes affect the pulmonary veins and heart chambers equally. Sometimes a clearly split second heart sound becomes single or more closely split on inspiration (Fig. 1). Such paradoxical behaviour of the second sound with respiration is due to reversal of the normal order of valve closure, pulmonary closure preceding aortic closure (Leatham, 1952). This auscultatory sign may be recognized in the neighbourhood of the pulmonary area and confirmed by phonocardiography. A study has been made of 40 cases in which paradoxical splitting of the second heart sound was recognized on clinical and phonocardiographic examination.

Method. The heart sounds were studied in simultaneous recordings taken from the pulmonary and mitral areas. The electrocardiogram and indirect carotid pulse were registered at the same time. High frequency records were used (Leatham, 1952) and measurements were made from the onset of the earliest high-frequency vibration recorded, tracings being made during held expiration. Additional phonocardiograms were made in the fourth or fifth left interspace close to the sternum in many cases to record splitting of the first heart sound, and records were taken during quiet respiration where possible. The aortic component of the second heart sound was identified in the records made at the pulmonary and mitral areas by its coincidence with the dicrotic notch of the carotid pulse (allowance being made for the delay in transmission of the arterial pulse to the carotid vessels). The pulmonary component was readily identified in records made at the pulmonary area but was absent from the mitral area records; it had no constant relation to the dicrotic notch. When splitting of the first heart sound was present the left- and right-sided components were identified where possible. These are probably caused by closure of the atrio-ventricular valves (Dock, 1933) and in normal subjects mitral closure is slightly before tricuspid. The tricuspid element is loudest at the left sternal edge in the fourth or fifth space and the mitral element at the apex. Confirmation of mitral closure was obtained from the time of onset of the carotid pulse. A measure of the duration of right and left ventricular systole could then be made from tricuspid closure to pulmonary closure and from mitral closure to aortic closure.

RESULTS

The diagnoses in the 40 cases are listed (Table I). Further sound records were studied in order to determine the incidence of paradoxical splitting of the second heart sound in these conditions.

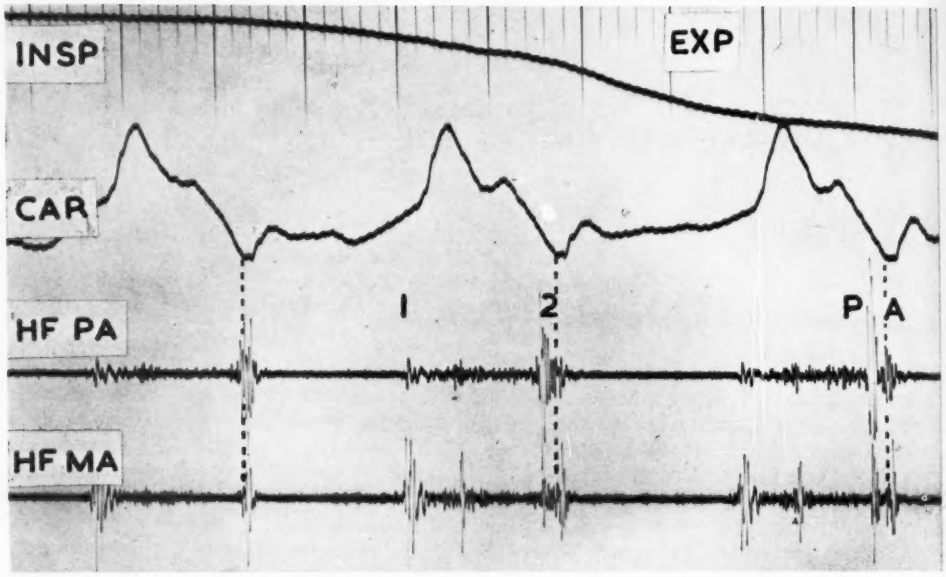

FIG. 1.—Paradoxical splitting of the second heart sound: effect of respiration. The sound is split by 0·04 sec. on expiration but is single on inspiration. This is due to prolongation of right ventricular systole during inspiration, the duration of left ventricular systole remaining constant throughout the respiratory cycle. (From a woman, aged 33, with a patent ductus: systemic pressure 150/62, PA pressure 115/60.)

In this and subsequent records the following abbreviations are employed. CAR=indirect carotid pulse. HF=high frequency. LF=low frequency. PA=pulmonary area. MA=mitral area. LSE=left sternal edge in fourth or fifth space. LD 2=standard lead II. 1 refers to first heart sound. 2 refers to second heart sound and letters P and A to its pulmonary and aortic components. Time markings are 0·04 and 0·2 sec.

TABLE I

CASES WITH PARADOXICAL SPLITTING OF THE SECOND SOUND

Diagnosis	No.
Left bundle-branch block	18
Aortic stenosis	10
Patent ductus arteriosus	10
Other conditions	2
Total	40

Left Bundle-branch Block. The delay of aortic valve closure in left bundle-branch block was described by Wolferth and Margolies (1935) and records of the heart-sounds contributed to the correct interpretation of the electrocardiogram in conduction defects (Battro *et al.*, 1938). Paradoxical splitting of the second heart sound was recorded in 18 out of 21 cases studied; in the other three, the heart sounds were not well enough recorded for analysis. The splitting of the second heart sound varied from 0·02 to 0·06 sec. on held expiration. The lateness of aortic valve closure was due in all cases to delay in activation of the left ventricle so that delay of mitral closure was always found where the first heart sound could be analysed (Fig. 2), and the onset of the carotid arterial pulse was correspondingly later (Fig. 3, Table II).

It is clear, therefore, that in left bundle-branch block the normal parity of the contraction times for the left and right sides is maintained. The delay of the aortic component of the second heart

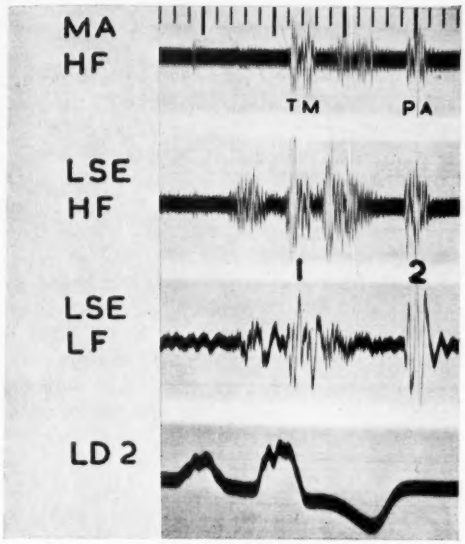

FIG. 2.—Complete left bundle-branch block. Tricuspid and mitral elements of the first heart sound are identified by the dominance of the tricuspid element in the record taken from the left sternal edge in the fourth space and of the mitral element in the trace from the apex. Mitral closure and aortic closure were further identified by their relation to the carotid pulse recorded on another tracing. There is a delay of 0·03 sec. in the onset of left ventricular contraction with a similar delay in aortic closure. (From a girl, aged 17, with mitral stenosis. QRS 0·16 sec. Record taken with held respiration.)

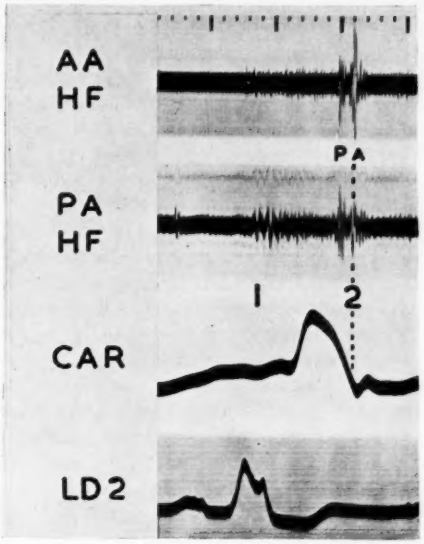

FIG. 3.—Complete left bundle-branch block, QRS 0·13 sec. Paradoxical splitting of second heart sound of 0·04 sec. A2 is recorded predominantly at the aortic area, and occurs 0·03 sec. before the dicrotic notch of the carotid trace, due to mechanical delay of the latter. (Record taken in held expiration.)

TABLE II

TIMING OF CARDIAC EVENTS IN LEFT BUNDLE-BRANCH BLOCK
(Mean of 18 cases)

Q–Mitral closure 0·11 sec. (±0·01) Normal, 0·06 sec. (±0·01)	R. ventricular systole (tricuspid closure–pulmonary closure) 0·30 sec. (±0·04)
Q–Tricuspid closure 0·07 sec. (±0·02) Normal, 0·08 sec. (±0·01)	L. ventricular systole (mitral closure–aortic closure) 0·30 sec. (±0·03)
Q–Carotid pulse* 0·16 sec. (±0·02) Normal, 0·09 sec. (±0·02)	Pulmonary–aortic closure 0·04 sec. (±0·01)

* Corrected for mechanical delay.

sound is a delay that affects the whole of left ventricular activity. A recognizable delay of aortic closure with paradoxical splitting of the second heart sound may be regarded as an essential clinical feature of left bundle-branch block.

Aortic Stenosis. As in pulmonary stenosis where prolongation of right ventricular systole and the low pulmonary arterial pressure result in a small late pulmonary component of the second sound, so in aortic stenosis aortic closure may be delayed. In pulmonary stenosis, however, extreme stenosis with a very low pulmonary arterial pressure is compatible with life and pulmonary closure may be delayed 0·10 sec. or longer. Such severe aortic stenosis is not encountered and so, although there may be prolonged left ventricular systole with paradoxical splitting of the second heart sound, the delay in aortic closure is shorter and less constant than is the delay of pulmonary closure in pulmonary stenosis.

Paradoxical splitting of the second heart sound varying from 0·01 to 0·06 sec. was found in 10 out of a total of 23 cases of aortic stenosis studied (Fig. 4 and 5). Normal splitting was found in five and the second sound was single in eight. A single second heart sound in aortic stenosis may be due to delay in aortic closure so that it coincides with pulmonary closure, to the pulmonary component being buried in the aortic systolic murmur (Leatham, 1954), or to aortic closure being so faint as to be inaudible. Hence a single second sound in aortic stenosis is frequently associated with prolongation of left ventricular systole.

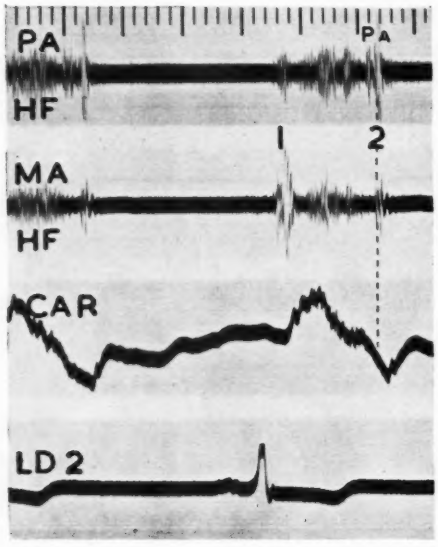

FIG. 4.—Aortic stenosis. Paradoxical splitting of second heart sounds recorded at PA. Aortic closure identified from its coincidence with dicrotic notch of carotid (mechanical delay of 0·03 sec.).

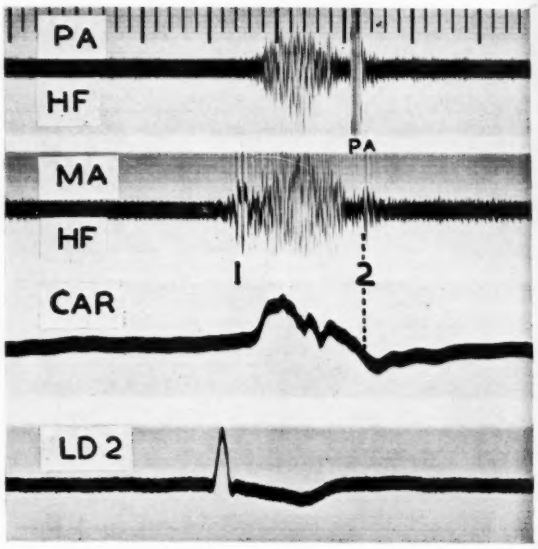

FIG. 5.—Aortic stenosis. Typical murmur is followed by paradoxical splitting of second heart sound, loud P2 in PA being followed by a small A2 (splitting is 0·04 sec.). (Record taken in held expiration.)

The timing of cardiac events in aortic stenosis with paradoxical splitting of the second sound (Table III) shows no delay in onset of left ventricular systole as judged from the times of mitral closure and upstroke of the arterial pressure pulse. Reversal of the order of aortic and pulmonary valve closure is due to left ventricular systole taking 0·04 sec. longer than right. The normal duration of ventricular systole shows considerable variation even when correction is made for the

TABLE III

TIMING OF CARDIAC EVENTS IN AORTIC STENOSIS WITH PARADOXICAL SPLITTING OF SECOND SOUND
(Mean of 10 cases)

Q–Mitral closure 0·07 sec. (±0·03)	R. ventricular systole 0·29 sec (±0·04): 0·32 sec.*
Q–Tricuspid closure 0·08 sec. (±0·03)	L. ventricular systole 0·33 sec. (±0·03): 0·36 sec.*
Q–Carotid pulse 0·10 sec. (±0·03)	Pulmonary–aortic closure 0·04 sec. (±0·02)

* Corrected to cycle length 1·0 sec. using formula: Corrected time = Measured time ÷ $\sqrt{}$ Cycle length (sec.) (Bazett, 1920).

heart rate. Mean left ventricular systole measured in 20 healthy subjects was 0·34 sec. (±0·02) when corrected for cycle length of 1·0 sec. Measurement of right ventricular systole during held expiration showed, however, that the durations of systole of the right and left sides in normal subjects were nearly always identical, mean right ventricular systole in this group also being 0·34 sec. (±0·02). Comparison of the duration of systole in aortic stenosis with paradoxical splitting of the second sound with the normal shows prolongation of left ventricular systole (0·36 sec.) and shortening of right ventricular systole (0·32 sec.). The former has been shown to be a feature of severe aortic stenosis (Katz and Feil, 1925) and is a result of obstruction to left ventricular outflow: the latter is difficult to explain but may be partly due to reduced systemic venous return.

The aortic stenosis was regarded as severe on other clinical grounds in eight of the ten cases in which paradoxical splitting was found. Normal splitting of the second sound was never found when the aortic stenosis was severe.

Patent Ductus Arteriosus. Paradoxical splitting of the second heart sound varying from 0·01 sec. to 0·07 sec. was found in 10 out of 29 cases of patent ductus (Fig. 1 and 6). The pulmonary component of the second sound was obscured by the murmur in three cases which had to be rejected, and of the remaining 16, splitting was normal in nine and the second sound was single in seven.

The paradoxical splitting is due, as in aortic stenosis, to a disparity between the duration of right and left ventricular systole. When these are corrected for heart rate in cases of patent ductus with paradoxical splitting there is found to be prolongation of left ventricular and shortening of right ventricular systole. The former change suggests increase in the diastolic size of the left ventricle (Wiggers, 1949), associated in patent ductus with overfilling from the excessive pulmonary flow. The shortened right ventricular systole may be due in part to reduced systemic venous return and possibly also to increased pulmonary diastolic pressure.

TABLE IV

TIMING OF CARDIAC EVENTS IN PATENT DUCTUS WITH PARADOXICAL SPLITTING OF SECOND SOUND
(Mean of 10 cases)

Q–Mitral closure 0·06 sec. (±0·01)	R. ventricular systole 0·27 sec. (±0·04): 0·31 sec.*
Q–Tricuspid closure 0·07 sec. (±0·02)	L. ventricular systole 0·31 sec. (±0·04): 0·35 sec.*
Q–Carotid pulse 0·10 sec. (±0·01)	Pulmonary–aortic closure 0·03 sec. (±0·02)

* Corrected for cycle length 1·0 sec.

Great variation is now recognized in the clinical and hæmodynamic findings in patent ductus according to the size of the communication and the pulmonary vascular resistance. The volume of the shunt and its direction might be expected to influence the second heart sound. Paradoxical splitting of the second sound was found in more than half the cases in which the shunt was from left to right (8 out of 15). It was found in only 2 out of 11 cases with severe pulmonary hypertension and balanced or reversed shunt. Measurements of pulmonary arterial pressure and pulmonary and systemic flow (Table V) suggested that when the pulmonary vascular resistance was low and the shunt small so that the pulmonary arterial pressure remained normal, the normal order of valve closure obtained. When the shunt was of greater magnitude and the pulmonary arterial pressure

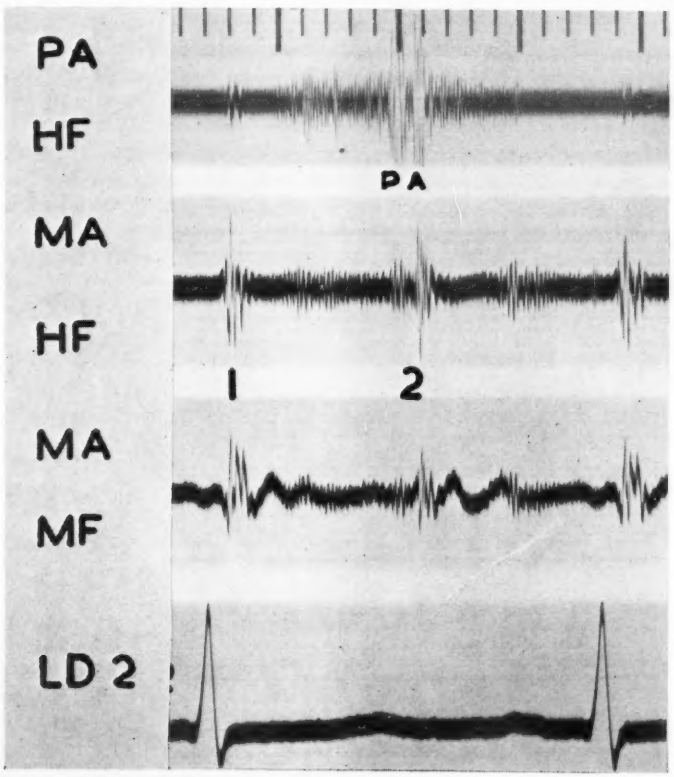

FIG. 6.—Patent ductus arteriosus. Continuous murmur recorded at PA. First heart sound is single. Paradoxical splitting of second heart sound recorded, A2 being identified by its presence at the MA and its relation to the dicrotic notch recorded on another tracing.

moderately increased paradoxical splitting commonly occurred. When the resistance was greatly increased so that there was no longer a left-to-right shunt the second sound was frequently single.

Other Cases. Paradoxical splitting of the second heart sound was heard and recorded in two further cases, one of hypertensive heart disease and one of mitral stenosis. Phonocardiograms of 10 other examples of each of these conditions were studied, in all of which the normal order of aortic and pulmonary valve closure was found. Paradoxical splitting of the second sound may therefore be regarded as exceptional in these conditions.

TABLE V

HÆMODYNAMIC DATA OF 23 CASES OF PATENT DUCTUS

	Normal splitting				Single second sound				Paradoxical splitting			
	Case and age	Pulmonary arterial pressure (mm. Hg)	Ratio of pulmonary to systemic flow	Total pulmonary vascular resistance (units)*	Case and age	PA pressure	P/S flow	PVR (units)	Case and age	PA pressure	P/S flow	PVR (units)
Left to right shunt	D.G. 16	12/5	1·6:1	0·2 u.					D.D. 4	35/22	2·5:1	2·0 u.
	M.P. 7	15/12	1·5:1	0·8 u.					M.P. 21	37/20	2·5:1	1·5 u.
	A.T. 47	18/5	2·0:1	0·5 u.					S.H. 8	42/29	1·5:1	4·0 u.
	C.H. 16	26/7	2·0:1	0·5 u.					T.N. 27	50/25	2·5:1	3·0 u.
	M.T. 4	65/25	3·0:1	4·0 u.					J.M. 22	65/35	2·5:1	—
									P.W. 5	85/50	5·0:1	4·0 u.
									I.S. 33	115/60	2·5:1	6·0 u.
Balanced or reversed shunt	J.G. 9	40 (mean)	1·0:1	10 u.	R.S. 10	66/52	1·0:1	12 u.	G.G. 6	100/65	1·0:1	20 u.
	S.L. 16	95/65	0·8:1	25 u.	D.B. 13	82 (mean)	1·0:1	15 u.	J.P. 37	110/60	0·7:1	20 u.
	J.P. 13	105/65	1·0:1	12 u.	P.W. 30	100/70	1·0:1	15 u.				
	D.B. 14	110/70	0·8:1	30 u.	W.K. 13	115/75	0·6:1	12 u.				
					M.M. 31	130/60	1·0:1	25 u.				

* Pulmonary vascular resistance calculated from formula

$$\frac{\text{Mean pulmonary arterial pressure} - \text{mean left atrial pressure (mm. Hg)}}{\text{Pulmonary blood flow (litres/min.)}}$$

Discussion

Careful auscultation over the base of the heart is necessary if paradoxical splitting of the second sound is to be recognized. Both components of the sound are generally best heard in the second left intercostal space but it is often easier to listen to them throughout the respiratory cycle in the third or even fourth space. The sign may escape recognition if respiration is noisy or if one of the components of the second sound is faint. Phonocardiography is of considerable value in these doubtful cases.

The sign was easily recognized in left bundle-branch block and it is possible to distinguish this from right branch block and from other causes of a widely split second sound with reasonable accuracy at the bedside. In aortic stenosis, the assessment of which may be difficult when mitral valve disease co-exists, the presence of a normally split second sound may be regarded as strong evidence against severe aortic stenosis, which should always be accompanied by a single or a paradoxically split second sound.

The presence of paradoxical splitting of the second sound in many cases of patent ductus is particularly interesting. This sign has not been found in any other form of left-to-right shunt. In doubtful cases it has proved a useful sign in establishing a clinical diagnosis. Its presence suggests a substantial left-to-right shunt with some elevation of pulmonary arterial pressure.

Summary

Reversal of the normal order of aortic and pulmonary valve closure may be recognized clinically by the closing up of a split second heart sound on inspiration and has been called paradoxical splitting of the second sound. This has been studied by phonocardiograms of 40 cases.

It was invariably found with left bundle-branch block and was due to delay in the onset of left ventricular systole.

It was found in 10 out of 23 cases of aortic stenosis. It was due to prolongation of left ventricular systole in the presence of a shortened right ventricular systole and was generally a sign of severe stenosis.

It was found in 10 out of 29 cases of patent ductus. This also was due to prolongation of left ventricular and shortening of right ventricular systole. It was usually found in cases with a substantial left-to-right shunt and a moderate increase of the pulmonary arterial pressure.

The mechanism of paradoxical splitting of the second heart sound is discussed and its value in bedside diagnosis assessed.

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THE INTRACARDIAC ELECTROGRAM AS AN AID IN THE LOCALIZATION OF PULMONARY STENOSIS

BY

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The intracardiac electrogram (*IEG*), as recorded from an electrode at the tip of a cardiac catheter, shows a striking contrast in pattern between that from the lumen of the pulmonary artery and that from the cavity of the right ventricle. The change is well seen in continuous records made during withdrawal of the catheter from the pulmonary artery through the pulmonary valve and is, in general, abrupt. Having regard to the importance of accurate pre-operative diagnosis of the site of the stenosis, and recognizing the artefacts that may complicate pressure tracings, it appeared to us that recording the *IEG* along with the pressure pulse during catheterization of patients with pulmonary stenosis might be useful in determining the site of the obstruction in the right ventricular outflow tract.

Material and Method

The *IEG* obtained from a catheter carrying a nickel-silver electrode on its tip was recorded optically on photosensitive paper together with limb- and chest-lead electrocardiograms, and pressure pulses (Emslie-Smith, 1955), the pressures being measured by a capacitance manometer. It was recorded during diagnostic catheterization of 43 patients. Of these, 19 were cases of pulmonary stenosis, simple or complicated. The remaining 24 included 18 with rheumatic heart disease, 1 with constrictive pericarditis, and 5 with congenital heart disease without pulmonary stenosis.

In most of the 19 patients with pulmonary stenosis, several recordings of pressure pulse and *IEG* were made during repeated withdrawal of the catheter from the pulmonary artery to the right ventricle, to confirm that the change in pattern of the *IEG* at the pulmonary valve was reproducible in successive tests.

Results

General. In 4 of the 43 patients, the electrocardiogram showed ventricular arrhythmia as the catheter tip passed through the pulmonary valve, so that the characteristic change in the *IEG* was obscured. In 37 of the other 39 the change in form of the *IEG* at the pulmonary valve was abrupt. In two patients the change in the form at this level was much less abrupt; both had right bundle-branch block. There were, however, several cases of right bundle-branch block among the 37 showing an abrupt transition.

Pulmonary Valvular Stenosis (abrupt change in *IEG* synchronous with rise in systolic pressure at pulmonary valve). In 15 patients the clinical diagnosis was pulmonary valvular stenosis with intact ventricular septum; several of them had proven or suspected atrial septal defects. All had some symptoms referable to the heart disease, although they were handicapped to varying degrees. The resting right ventricular systolic pressures ranged from 23 to 170 mm. Hg. Seven had marked post-stenotic dilatation of the pulmonary artery radiologically. The only patient who was cyanosed at rest had severe pulmonary stenosis probably with an atrial septal defect, and improved considerably following pulmonary valvotomy. No patient had digital clubbing.

Fig. 1 and 2 show the typical pattern of pressure pulse and *IEG* in pulmonary valvular stenosis. A marked and, in some cases, dramatic rise in systolic pressure is recorded simultaneously with an abrupt change in the form of the *IEG*.

Recognition of the Venturi Effect in Pulmonary Valvular Stenosis. By contrast with Fig. 1 and 2, Fig. 3, also from a patient with pulmonary valvular stenosis, shows marked pressure oscillations during the withdrawal of the catheter and before the right ventricular pressure is recorded, suggesting, at first sight, the pressure tracing of infundibular stenosis. These pressure pulses, however,

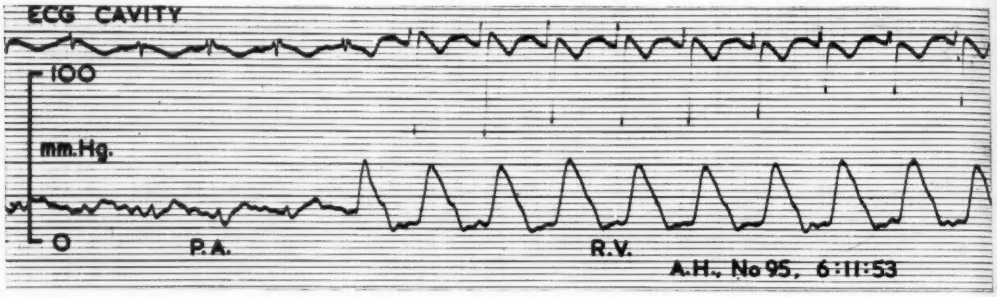

FIG. 1.—Pulmonary valvular stenosis with intact ventricular septum. The catheter tip has passed back through the pulmonary valve during ventricular systole and the first right ventricular pressure pulse is incomplete; the corresponding complex of the *IEG* shows only minor T wave change as compared with the complexes recorded from the lumen of the pulmonary artery. The subsequent full right ventricular pressure pulses are accompanied by *IEG* of right ventricular type. A.H., aged 6 years.

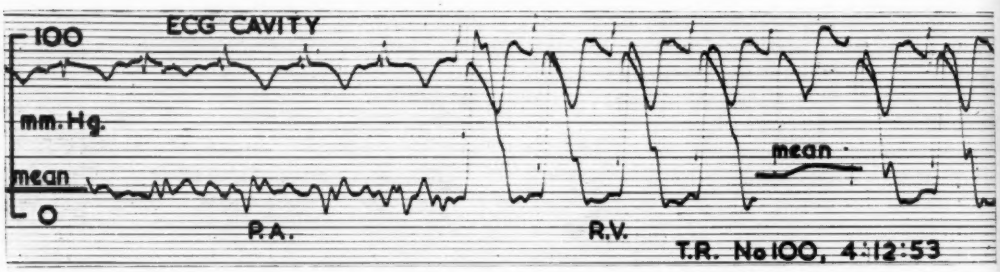

FIG. 2.—Pulmonary valvular stenosis with intact ventricular septum. The catheter tip has passed through the pulmonary valve during ventricular diastole and, synchronous with the recording of the first full right ventricular pulse there is an abrupt change in the *IEG* to right ventricular type. T.R., aged 9 years.

are recorded from the main pulmonary artery and show a *fall* instead of a rise during systole, as is obvious from the synchronous *IEG* tracing. They are, in fact, the "negative pressure waves" that have been ascribed by Sobin *et al.* (1954) to the Venturi effect produced by the high velocity jet of blood forced through the stenosed pulmonary valve. It will be noted that in the *IEG* tracing, the first complex of right ventricular pattern, with deeply inverted T wave, was recorded synchronously with the first full right ventricular systolic pressure wave, confirming the valve as the site of the stenosis. This patient showed characteristic post-stenotic dilatation of the pulmonary artery. In another patient with severe pulmonary stenosis, we recorded negative pressure waves of an amplitude of 40 mm. Hg in the main pulmonary artery (Fig. 4). Again the *IEG* confirmed that the stenosis was valvular.

Recognition of Positive Pressure Artefact in Main Pulmonary Artery, in Pulmonary Valvular Stenosis. In three patients the diagnosis was Fallot's tetralogy. Records from one of these patients

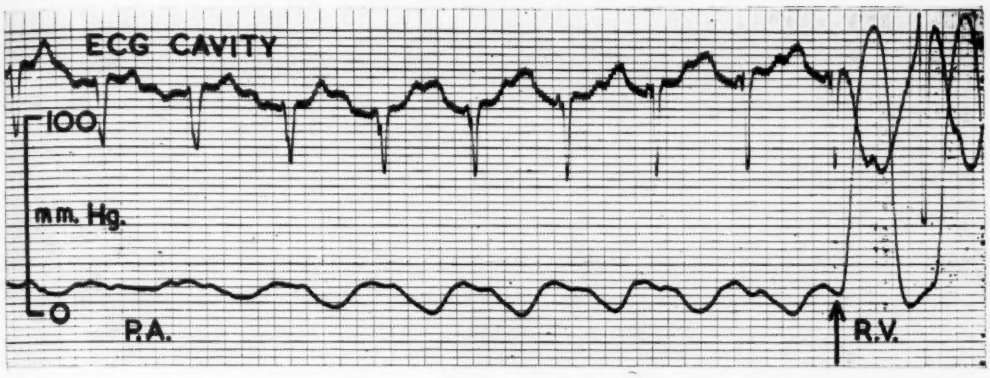

FIG. 3.—Pulmonary valvular stenosis with intact ventricular septum and marked post-stenotic dilatation of main pulmonary artery. As the catheter tip is withdrawn down the main pulmonary artery towards the pulmonary valve there appears a systolic pressure dip—this should not be confused with the diastolic pressure dip recorded when the catheter tip passes through a normal pulmonary valve. The passage of the catheter tip through the pulmonary valve is shown by the abrupt change in form of the *IEG* which is synchronous with a large right ventricular pressure pulse. I.S., aged 14 years.

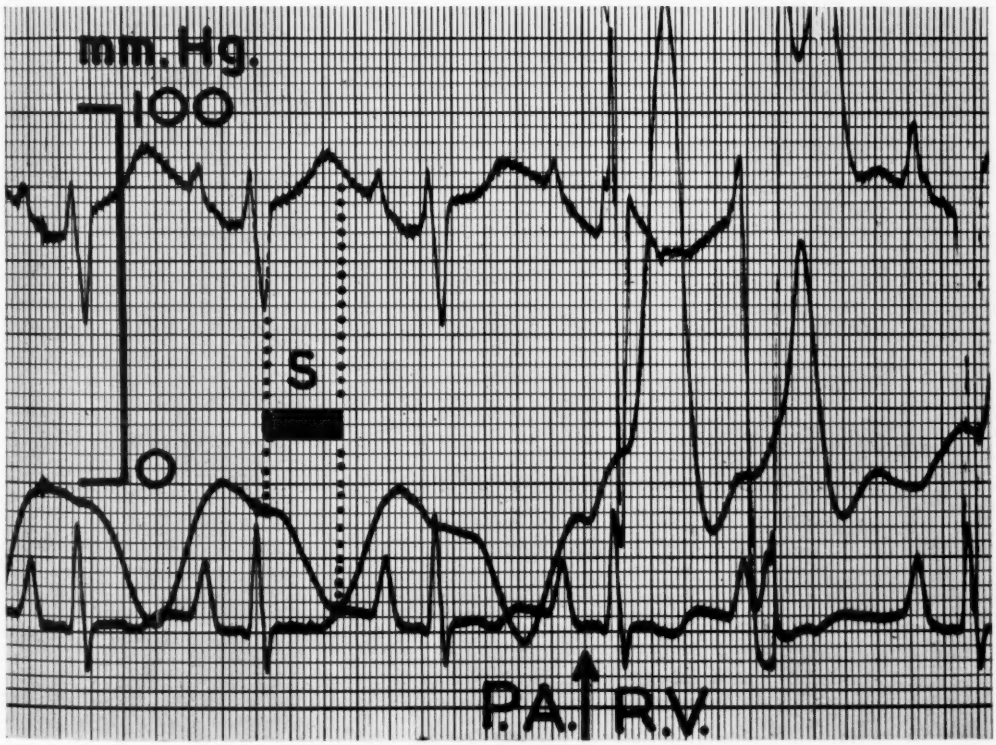

FIG. 4.—Pulmonary valvular stenosis with intact ventricular septum. The tracings from above downwards are: *IEG*, pressure pulse, and standard electrocardiogram lead II. S=systole. Note the systolic pressure dip in the main pulmonary artery and the change in *IEG* as the first right ventricular pulse is recorded. J.M., aged 11 years.

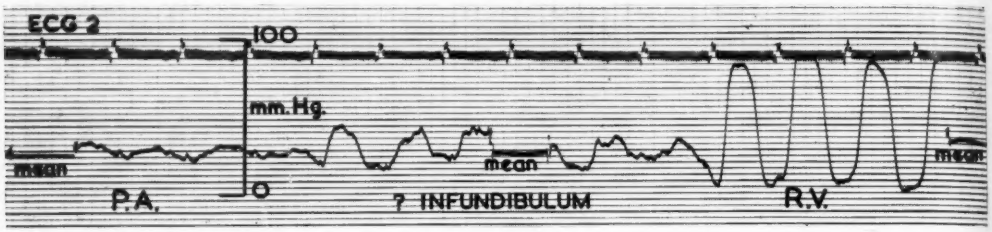

FIG. 5.—Fallot's tetralogy. Tracing obtained at cardiac catheterization in 1953. The provisional diagnosis was combined valvular and infundibular pulmonary stenosis. H.C., aged 5 years.

illustrate another possible fallacy in the localization of pulmonary stenosis from pressure tracings. When the first pressure tracing was recorded without an *IEG*, its form suggested combined valvular and infundibular stenosis (Fig. 5). Later, the manœuvre was repeated with an electrode-tipped catheter, permitting synchronous recording of pressure pulses and *IEG* (Fig. 6). It was noted that

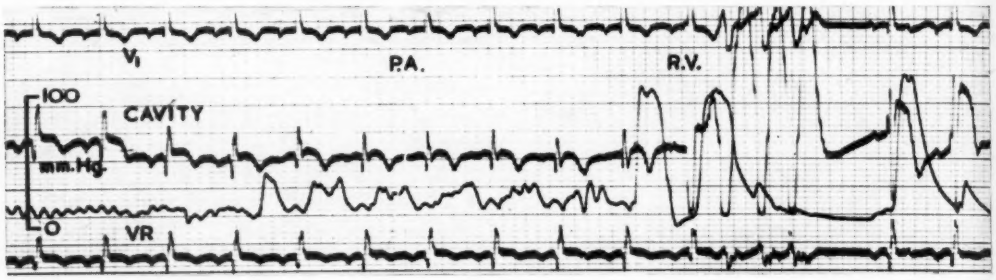

FIG. 6.—Cardiac catheterization repeated in 1955 20/1/55. Tracings from above downwards: electrocardiogram (V1), *IEG*, pressure pulse, and lead VR. Reading from left to right there is an increase in the amplitude of pressure pulse after the fourth QRS complex, without any accompanying change in the *IEG*. There is a minor change in the T wave of the tenth *IEG* complex synchronous with the first right ventricular pressure pulse. There follow four ventricular ectopic beats. The succeeding sinus beat shows the right ventricular type of *IEG* complex. Pulmonary valvular stenosis (as part of a Fallot's tetralogy) was therefore diagnosed and this was confirmed at pulmonary valvotomy.

an abrupt change in the *IEG* did not occur before the appearance of the larger systolic pressure waves of nearly 100 mm. Hg amplitude. The much smaller rise in systolic pressure, seen in the left-hand side of Fig. 6, therefore occurred distal to the pulmonary valve. Valvular pulmonary stenosis was diagnosed as the only obstruction to the right ventricular outflow tract, and this was confirmed at operation when valvotomy was successfully performed. At the second catheterization it had been noted that, with simultaneous screening of the heart and monitoring of pressure pulse and *IEG* on the oscilloscope, the larger pulmonary systolic pressure waves were seen when the tip of the catheter lay in the main pulmonary artery and the amplitude diminished markedly when the catheter tip entered the right or left main branch. The increased amplitude of the pressure pulse in the main pulmonary artery may have been caused by pressure artefact due to vigorous movement of the catheter along the axis of its tip (Wood *et al.*, 1954).

The IEG in Infundibular Stenosis. The last patient with pulmonary stenosis was an asymptomatic 16-year-old girl with a widespread harsh systolic murmur and thrill, maximal at the left sternal border in the third and fourth interspaces. Cardiac catheterization showed that she had a ventricular septal defect with left-to-right shunt. In addition, a systolic pressure gradient was demonstrated, during the passage of the catheter through the body of the right ventricle (Fig. 7). The manœuvre

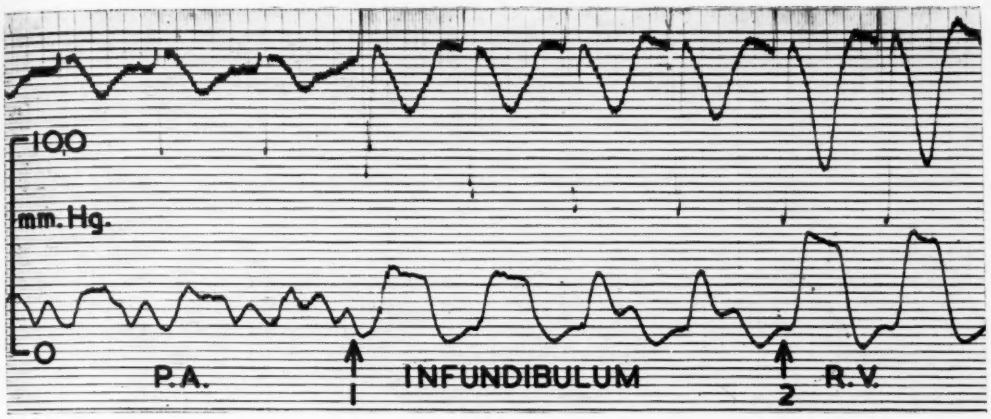

FIG. 7.—Pulmonary infundibular stenosis with ventricular septal defect (left-to-right shunt). Recording of pressure pulses and *IEG* at cardiac catheterization. At the first arrow there is a small systolic pressure gradient synchronous with a change in the *IEG* to right ventricular type. At the second arrow, there is a further systolic pressure gradient with little further change in *IEG*. Similar tracings were obtained on three separate withdrawals of the catheter from pulmonary artery to right ventricle. The tracings suggest infundibular stenosis. C.T., aged 16 years.

was repeated several times and this systolic pressure gradient was a constant finding. From simultaneous screening and monitoring the pressure pulse and *IEG*, it was thought that there was an infundibular stenosis about one inch below the pulmonary valve. Anatomical proof of this case, however, is lacking.

DISCUSSION

The interpretation of pressure pulse tracings recorded during cardiac catheterization of patients with pulmonary stenosis is often difficult. In the first place, the systolic pressure change should be abrupt and of impressive size (Shephard, 1954). To be significant, positive pressure pulses should be systolic in timing. Thus, careful inspection will detect those pressure pulses that are negative during systole and are caused by the tip of the catheter lying in the high velocity jet of blood flowing through the pulmonary valve (Sobin *et al.*, 1954). Conversely, not all positive systolic pressure pulses are free of artefact for Wood *et al.* (1954) have demonstrated positive pressure increments in the pulmonary arterial pressure pulse due to forward movement of the catheter tip in systole. We have found the *IEG* to be of help in the interpretation of the pressure pulse tracings since, as we have shown, the abrupt change in form of the *IEG* recorded from the catheter electrode is generally a signal of its passage through the valve. If such an abrupt change in form is synchronous with a significant rise in systolic pressure during withdrawal of an electrode-tipped catheter, valvular stenosis can be diagnosed with reasonable confidence.

On the other hand, during withdrawal of a catheter in a patient with infundibular stenosis, one may expect the abrupt change in form of the *IEG*, signalling the passage of the tip through the valve, to precede the rise in systolic pressure occurring at the junction of infundibulum and main right ventricular cavity.

SUMMARY

When an electrode-tipped cardiac catheter is withdrawn from the pulmonary artery back into the right ventricle, an abrupt change in form of the intracardiac electrogram usually occurs at the region of the pulmonary valve. Simultaneous recording of the intracardiac electrogram and

pressure pulse in patients with pulmonary stenosis is thus of help in locating the level of the stenosis. In valvular stenosis the systolic pressure gradient is related to the abrupt change in form of the electrogram. Artefacts in the pressure tracing that can lead to a wrong diagnosis of valvular stenosis as infundibular stenosis are negative pressure waves due to Venturi effect and, possibly, systolic pressure increments due to catheter movement, when the catheter tip lies just beyond the pulmonary valve. Such errors in diagnosis may be obviated by correlation of pressure pulse and intracardiac electrogram. In infundibular stenosis, during withdrawal of the catheter the abrupt change in form of the intracardiac electrogram, signalling passage through pulmonary valve, should precede the rise in systolic pressure occurring at the junction of infundibulum and main right ventricular cavity.

We are grateful to Dr. C. Pickard, Consultant Radiologist, Dundee Royal Infirmary, and members of his staff for their interest and co-operation in this work; to Professor D. M. Douglas for the operative findings in the two cases quoted; and to the staff of the Department of Medicine for secretarial and photographic assistance.

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RADIOLOGICAL KINETICS AND PULMONARY ARTERIAL PRESSURE IN CONGENITAL HEART DISEASE*

BY

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The movements of the pulmonary artery can be observed clinically only if certain modifications of the radiological methods are employed. Fluoroscopy allows only a personal subjective observation which is therefore subject to criticism. Radiokymography and electrokymography, on the other hand, provide tracings that render an objective and detailed study possible, not only in respect of the shape of the tracings but of their time relation. These tracings can be preserved, reproduced, published, and compared. Similarly, analysis of intra-arterial pressure curves recorded in the course of cardiac catheterization gives information regarding the circulatory conditions in this vessel and especially regarding the hæmodynamics.

We have applied these investigations on the kinetics and hæmodynamics of the pulmonary artery in a certain number of cases of congenital heart disease and have analysed the results; the idea appears new to us for we have not found any references to this subject. The references given at the end of the paper are to publications dealing simply with electrokymography.

One should, to begin with, emphasize that *a priori* the comparisons which we have studied, though they relate to two very different phenomena, are not comparisons of fundamentally different nature.

In studying the kinetics of the pulmonary artery, we are dealing with the displacements of its contours that are visible radiologically. These may be only transmitted pulsations but we think that in the great majority of cases they actually correspond to an arterial pulse, that is to say to the succession of expansion and retraction of the vascular wall (change of volume) during the passage of each pulse beat. These vascular pulsations observed and recorded radiologically are, in fact, conditioned by ventricular activity. The vigorous contraction of the ventricle, of good tone and well filled, produces a wave of considerable amplitude and in turn a marked pulsation, but this only on condition that there is no obstacle to the free passage of the blood stream and that no shunt reduces it by a fraction. This pre-supposes at the same time a perfect arterial elasticity which is able to absorb and then restore part of the kinetic energy that has been liberated. Conversely, the loss of elasticity slows the wave and reduces the amplitude of the pulsations; in its extreme form complete rigidity would be associated with complete absence of pulsation in the artery. From these considerations it follows that a large amplitude of pulsation is evidence of a large arterial output running freely through elastic vessels.

* Travail du: Centre médico-chirurgical des affections cardiovasculaires de l'Hôpital Broussais-la-Charité; Clinique Cardiologique: Professeur E. Donzelot et collaborateurs: R. Heim de Balsac, M. Durand, C. Metianu, J. E. Escalle, R. Guillemot, V. Serafini, P. Kervoelen, J. Bougnoux, J. Bernath, P. Samuel et E. Beyda; Clinique Chirurgicale: Professeur F. d'Allaines, J. Lortat-Jacob, Ch. Dubost et collaborateurs: N. du Bouchet, J. Le Brigand, M. Allary, J. Vaysse, J. Passelecq, J. Guery, F. Brunet d'Aubiac et J. Elmelik et Service Central d'Electroradiologie: Docteur F. Foubert.

In similar fashion the intra-arterial pressure results from the force of contraction and the ventricular capacity, given normal arterial elasticity and provided no obstruction or shunt is placed in the circulatory circuit. An obstruction such as a stenosis raises the pressure behind it and depresses it distally. A shunt modifies the currents in variable fashion, determined by the interplay of pressures to which it leads. The arterial elasticity comes into play in the sense that to maintain an equal output through a more rigid vessel demands a raised pressure.

The kinetics and the pressures are thus two different phenomena but often they are in close relation to the flow. Now this idea of flow is precisely the predominant one in the particular types of congenital heart disease we have studied. Apart from the physio-pathological methods that allow its measurement, the flow is determined by various factors, and it is certainly not without interest to take these into consideration.

Material. The material studied consists of patients who have been subjected at the same time to electrokymography of the pulmonary arterial movements following the technique described by Donzelot *et al.* (1955), and to registration of their intra-vascular pressure by the customary method of cardiac catheterization. The use of standard methods allows us to dispense with a description of the apparatus or the technique used in the course of these two investigations. We would emphasize only that the two examinations have not been made simultaneously, but have been made on the same subjects, at intervals of a few days. The two tracings, therefore, whose characters we are about to compare, have not been recorded synchronously, but their analysis is made with reference to the electrocardiogram of which the same leads have been recorded with the electrokymogram and with the pressure curve. We hope, in future studies, to be able to record an electrical polygram, hæmodynamic and kinetic, a project that requires only a judicious blending of the different methods of registration.

Our researches have been carried out on 40 patients, of whom 13 had pulmonary stenosis (or trilogy), 8 tetralogy of Fallot, 15 atrial septal defects, 2 patent ductus, and 2 Eisenmenger's complex.

Results

I Comparison of the Electrokymogram and Pulmonary Artery Pressure Curves in Normal Subjects

In normal subjects the registration radiologically of the movements of the pulmonary artery does not entail any difficulty. This may not apply to cardiac catheterization which we only carry out when the patient is considered to be able to profit directly from this special investigation. In the absence, therefore, of catheterization in normal subjects, we have used the tracings of normal pressures from young subjects whose cardiac lesion had not progressed enough to affect their pulmonary arterial tree.

The normal pulmonary artery electrokymogram has the same appearance as an ordinary arterial tracing with a sharp upstroke in systole (Fig. 1), a crest of somewhat variable form and a slower (more oblique) diastolic descent marked by a notch synchronous with the closure of the semilunar valves (cf. Donzelot *et al.*, 1955).

The curve of pulmonary artery pressure has a form that can be superimposed on the other (Fig. 1). We find the same general form of curve and the same detail. The inclination of the upslope is similarly from 10° to 20° while the diastolic descent is at 30° to 45°, while the diastolic notch occurs about the middle third. In general, however, the foot of the upstroke is usually marked by a rebound or a little diphasic wave (the taking up of tension equals the isometric phase) which is not inscribed in the electrokymogram. Otherwise all the details have a similar character. They are delayed in relation to the electrokymogram by several hundredths of a second. The friction of the column of blood against the walls of the catheter, the friction of the liquid column in the lead tube, and the inertia of the apparatus suffice to explain the slight asynchronism.

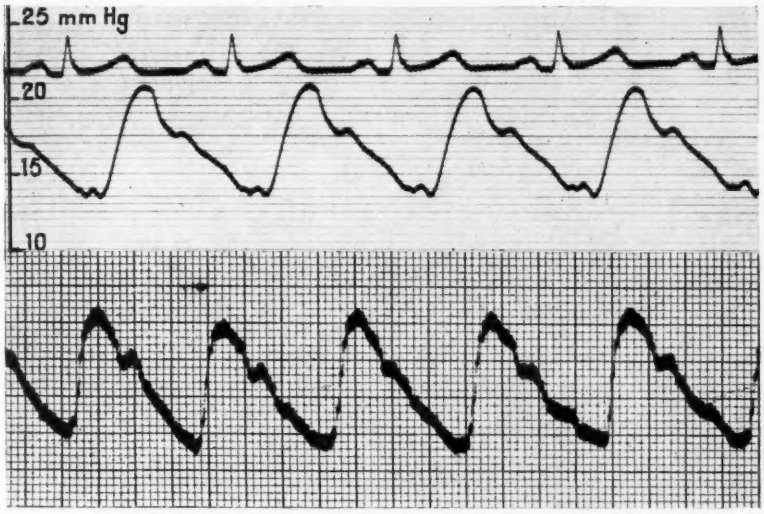

FIG. 1.—In the normal subject, the shape of the electrokymogram (below) and that of the pressure curve (middle tracing) can be superimposed, but the latter shows a slight delay due to the inertia of the recording apparatus.

II COMPARISON BETWEEN THE ELECTROKYMOGRAM AND PULMONARY ARTERY PRESSURE CURVES IN SOME CASES OF CONGENITAL HEART DISEASE

It is convenient to distinguish among congenital heart lesions those which imply increased and diminished pulmonary flow. The Eisenmenger complex will therefore be considered separately.

Congenital Heart Disease with Decreased Pulmonary Flow

As we have published elsewhere (Donzelot *et al.*, 1955) considerable modifications of the electrokymogram appear in cases of pulmonary valvular stenosis (Fig. 3): the beginning of the upstroke in systole may be delayed; the upstroke itself slower, appearing more oblique; the amplitude of the tracing reduced; the systolic-diastolic summit *en dôme*, in plateau, or even in a concave plateau (Fig. 3); and the diastolic notch diminished. All these pathological features are less in stenosis of slight degree and tend to disappear after a successful pulmonary valvotomy. In the tetralogy of Fallot, where the stenosis is more often infundibular, the curves lose entirely their frank arterial character, and are reduced to vague systolic undulations (Fig. 5). One can say, therefore, that the electrokymogram of pulmonary stenosis appears in different forms, the interpretation of which, although difficult, can afford valuable information on the degree of the stenosis, on the efficiency of the valvotomy (by comparison with tracings made before and after operation), and in a less decisive manner on the anatomical form, i.e. on the exact location of the stenosis.

The pressure curves also are very much modified. The pulmonary artery pressure in general is low and the form of the curve is not that of the usual arterial sphygmogram. Its amplitude is reduced and in extreme cases is limited to undulations of various form, in which one no longer recognizes either the sharp systolic upstroke or the slower diastolic fall (Fig. 2). If the stenosis is less marked, the alterations are less drastic, but in all the cases the pressure traces in relation to the kinetic traces show slight delay which is due, as in normal subjects, to the friction already described and to the inertia of the apparatus.

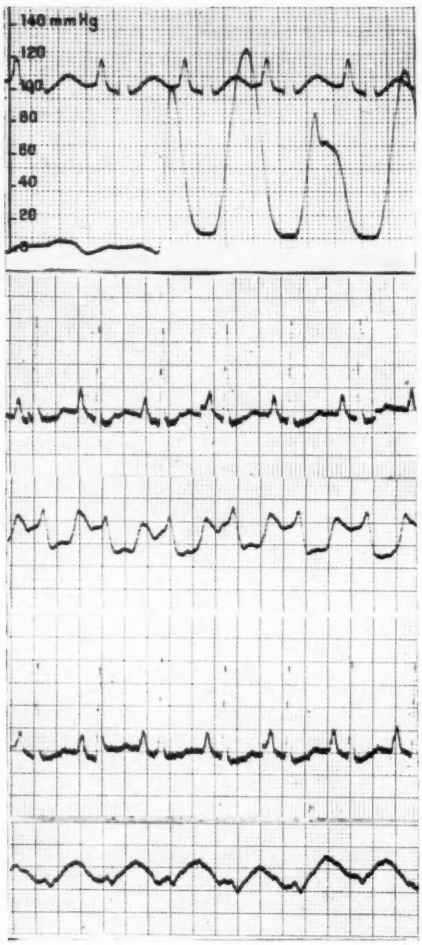

FIG. 2.—In a subject, suffering from an isolated infundibular stenosis verified at operation, the pressure curve (above) shows a sudden transition between the pulmonary artery and the right ventricle. The electrokymogram from the level of the middle arch (middle tracing) is retarded, lower in amplitude, and has a concave plateau. The electrokymogram at the level of the left pulmonary artery (below) is of smaller amplitude, delayed, and of indefinite form.

On the other hand, a most important contrast is yielded by the striking pressure gradient that exists between the low pressures of the pulmonary artery and the very high pressure of the right ventricle (Fig. 2 and 5). This discrepancy between the pressures in the two neighbouring chambers indicates that there is an obstruction between them which is difficult to overcome and reduces at the same time both the flow and the pressure on the distal side.

Can one get any further information from catheterization? Yes, in certain cases, when the catheter is withdrawn slowly from the pulmonary artery into the right ventricle, one sees on the tracing a double transition (Fig. 4). Following the small arterial pulsations and the low pressure in the pulmonary artery there suddenly appear waves of larger amplitude with higher summits and then a second transition leads to pulsations of large amplitude (systolic pressure very high and diastolic pressures low); the catheter is now in the right ventricle. This appearance, when it is well marked, is of itself certain evidence. It corresponds to the existence of an infundibular chamber bounded by the two stenoses, the one valvular and the other infundibular. It allows one to diagnose

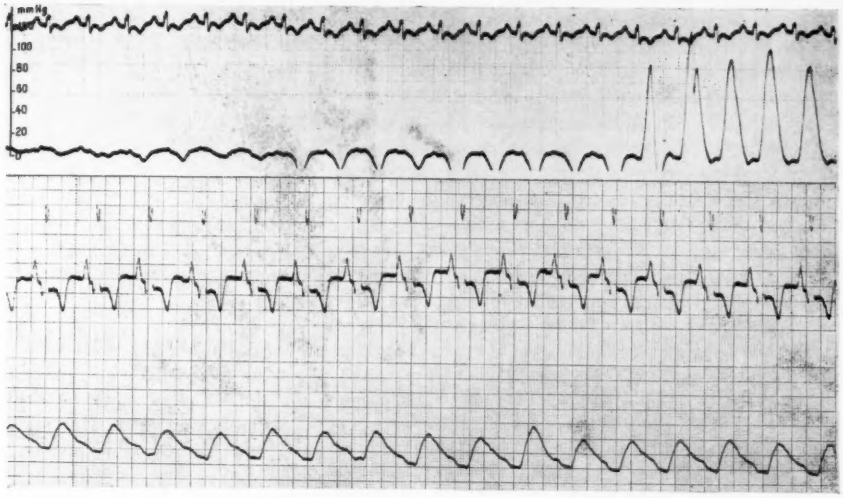

FIG. 3.—Pulmonary valvular stenosis. The pressure curve (above) shows a sudden transition preceded by a zone of negative pressures (aspiration phenomenon: the tip of the catheter lies exactly at the level of a valvular stenosis of diaphragm type). The electrokymogram registered from the upper part of the middle arch (below) shows large pulsations of typical arterial form but delayed in all respects. A successful valvotomy was carried out shortly afterwards.

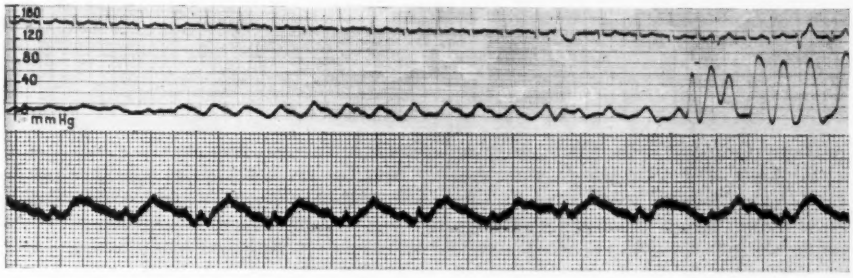

FIG. 4.—Double pulmonary stenosis (infundibular and valvular) in the tetralogy of Fallot. The pressure curves (above) show a double transitional zone (reduced to one-half). The electrokymogram from the middle arch (below) is of small amplitude and indeterminate form. (Scale 1/1.)

the existence of a double stenosis, but such an eventuality cannot be objectively demonstrated constantly and with precision in every case in which there is in fact a double stenosis.

In the majority of cases, on withdrawing the catheter from the pulmonary artery to the right ventricle, the records show a sudden transition that does not extend beyond a single cardiac cycle; the obstruction has been crossed at a single step. But this appearance, while indicating with certainty the presence of a stenosis, does not localize its site; the form of the curve is the same whether one is dealing with a valvular stenosis (Fig. 3) or a narrowing of the infundibulum (Fig. 5).

It is in fact the comparative study of the electrokymogram that enables us to bring a new precision to this matter. Actually the analysis of our tracings seems to establish this fact: when cardiac catheterization shows a sudden and single transition between the pulmonary artery and the right ventricle, the electrokymogram of a valvular stenosis (with a diaphragm type of sigmoid apparatus) recorded from the level of the middle arch or at the origin of the left pulmonary artery comprises

pulsations that are certainly delayed and as certainly of reduced amplitude, but always of an arterial form (Fig. 3), with a very characteristic modification—the flattening in a dome-shaped manner of the systolic peak of the curve. In every case in which these two findings have been combined, operation or post-mortem verification has confirmed that the stenosis was of valvular type. They were all cases of pure pulmonary stenosis or of Fallot's trilogy.

If, on the other hand, and with the same types of pressure curves, the electrokymogram consists of a series of less marked undulations of smaller amplitude, and now without a frank relationship between their form and the electrical sequence, the stenosis is infundibular (Fig. 5). Thus, in one of our patients who presented as a pure pulmonary stenosis and where catheterization had shown a marked pressure gradient between the pulmonary artery and the right ventricle with a single such transition, and where the electrokymogram was uninterpretable, valvotomy was decided upon. The operation showed the case to be one of very low infundibular stenosis.

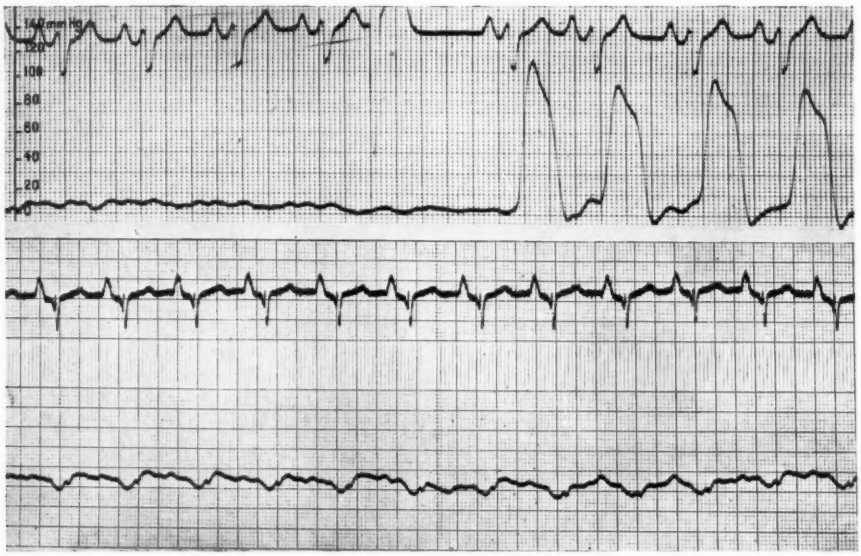

FIG. 5.—Tetralogy of Fallot. Above, sudden transition between the pressures in pulmonary artery and right ventricle. (The patient developed complete right branch block in the course of the catheterization.) Below, the electrokymogram of middle arch (below) which is of small amplitude and indeterminate form does not allow exact diagnosis of the seat of the stenosis. An aorto-pulmonary anastomosis has greatly improved the condition of the patient.

This appearance of the electrokymogram is unfortunately common to cases of infundibular stenosis and to those which are double without showing the double transition of a well-developed chamber between the strictures (Fig. 5). In such cases, therefore, the diagnosis of the anatomical deformity or of the seat of the stenosis cannot be determined and some doubt persists. Considered separately the kinetic tracings and the pressure curves have each certainly some value, but the juxtaposition seems to us capable of affording important diagnostic precision in a certain number of cases, information that is of capital importance in deciding on the type of surgical approach.

Congenital Cardiac Lesions with Increased Pulmonary Flow

(*a*) *Patent Ductus.* In cases of persistent ductus arteriosus the electrokymogram of the main trunk (middle arch) or left branch of the pulmonary artery permits recognition of two specific signs:

the rounding off, often *en dôme*, of the end of the systolic upstroke and the appearance of an unusually early diastolic rebound occurring in the first third or first half of the diastolic descent (Fig 6).

These characteristics have been found by us also in tracings of the intra-pulmonary arterial pressure. The curve of the change of volume (electrokymogram) and the pressure curve are in fact superimposable. Immediately after tension has been taken up in the ventricular wall, the systole shows a sudden ascent or upstroke, then it falls away to the right without any rebound notch to mark the transition. The whole contour of the tracing remains in fact of arterial form but with a broadened, rounded, dome-shaped summit. In a similar way the diastolic rebound often appears very large and its timing is early; this fact appears to us to be seen most clearly when there is pulmonary hypertension with a large flow through the persistent ductus (Fig. 6).

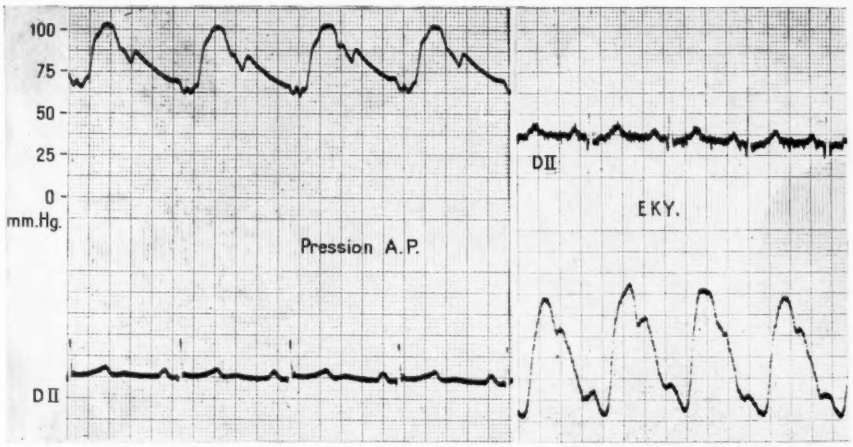

FIG. 6.—Patent ductus arteriosus. Tracings of pressure and electrokymogram have the same form; notch on the first third of the downstroke.

The late arrival of the aortic wave reaching the pulmonary artery at the end of systole and provoking, through the rise in pressure that it causes, a premature closure of the semilunar valves seems to us to be the origin of the two pulmonary artery phenomena that have been described. Change of volume and arterial pressure, in fact, proceed with remarkable parallelism.

(*b*) *Atrial Septal Defect.* The electrokymogram is of large amplitude and frequently shows a double diastolic rebound. The pressure curves show two inconstant characters; a rounded or even dome-shaped curvature of the systolic summit and it may be a double diastolic rebound.

What can one conclude from comparison of these tracings? The amplitude of the electrokymogram corresponds without doubt to marked over-filling of the pulmonary artery which is caused by an abnormally large input. A certain relation exists between this exaggeration of the pulmonary arterial pulsation and the increased inflow in the lesser circulation. But, as we have stated (Donzelot *et al.*, 1955), the electrokymographic method is not favourable for a measured or exact estimation of amplitude. Further in the case of atrial septal defects, the pulmonary artery pressures are variable, and to such a point that no constant relationship has been established between the height of the pressure and the estimated flow.

But one impression is gained from our observations; it seems that there is a relation between the level of the pressure and the amplitude of pulsation. With equal flow a large kinetic tracing would go hand in hand with low, i.e. normal pressures (Fig. 7), while with high pressures the corresponding pulsations are of smaller amplitude (Fig. 8). A more detailed study on a larger number of cases

would appear to us necessary to confirm these facts; but they seem to us logical, for the amplitude of beats corresponds to marked volumetric changes during the passage of each systolic wave and this implies good arterial elasticity and considerable variations between systolic and diastolic pressures. A high pressure raises as a rule both systolic and diastolic pressures, the latter proportionately more; the arterial system that is subjected to a continued abnormally high pressure tends, in general, to undergo modifications of its walls which become thickened and by a double anatomical and functional process more rigid.

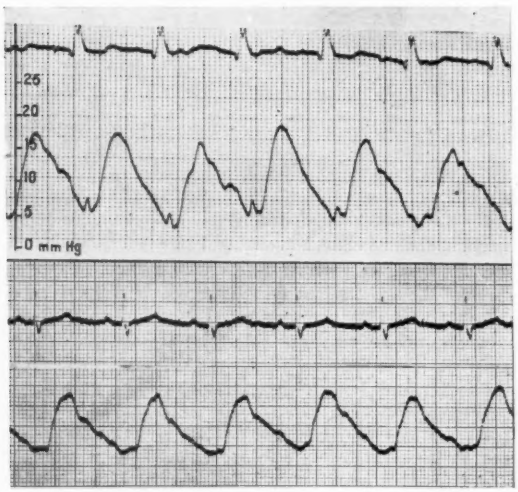

FIG. 7.—Atrial septal defect without pulmonary hypertension. The electrokymogram of the left pulmonary artery (below) and the pressure curve (above) have identical form. The pulmonary arterial pressure is not raised, the beats are of large amplitude. (In the course of the catheterization the patient developed a transient complete right branch block.)

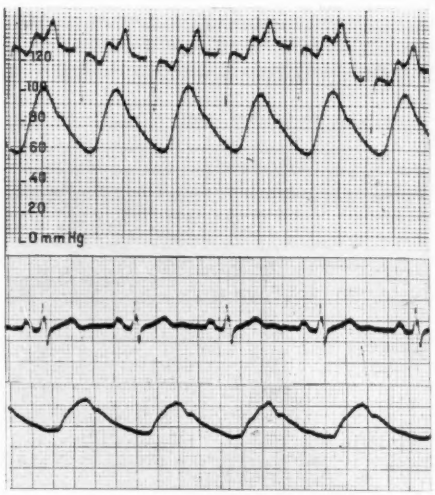

FIG. 8.—Atrial septal defect with pulmonary hypertension. The shape of the curves is identical but the raised pressure (above) is accompanied by a smaller amplitude of pulsation in the left main branch of the pulmonary artery (below).

(*c*) *Eisenmenger's Complex.* This congenital defect is not common and we have only examined two cases. Such limited observations do not allow us to draw hard and fast conclusions. The electrokymogram seems sufficiently characteristic; a horizontal plateau taking up the second half of systole (Fig. 9).

The pressure curves are more typically arterial but the end of systole is a little prolonged. The diastolic notch comes early and the diastolic downstroke is at first steep and then more gradual. Further, systolic and diastolic pressures are somewhat approximated and set at a high level.

SUMMARY AND CONCLUSIONS

A comparative study is reported of the radiological kinetics and pulmonary arterial pressures in 40 patients suffering from various forms of congenital heart disease.

In congenital heart disease with decreased pulmonary flow (21 patients; 13 simple pulmonary stenosis and 8 tetralogy of Fallot) comparison of the tracings shows the existence of two different alterations in the electrokymogram, either reduced amplitude *en dôme*, or a series of small undulations without any relation to the electrical events in the cardiac cycle. The comparison of the two types of tracing warrants the conclusion that in the first case there is pulmonary valvular stenosis and in the second case, a double stenosis, valvular and infundibular or infundibular.

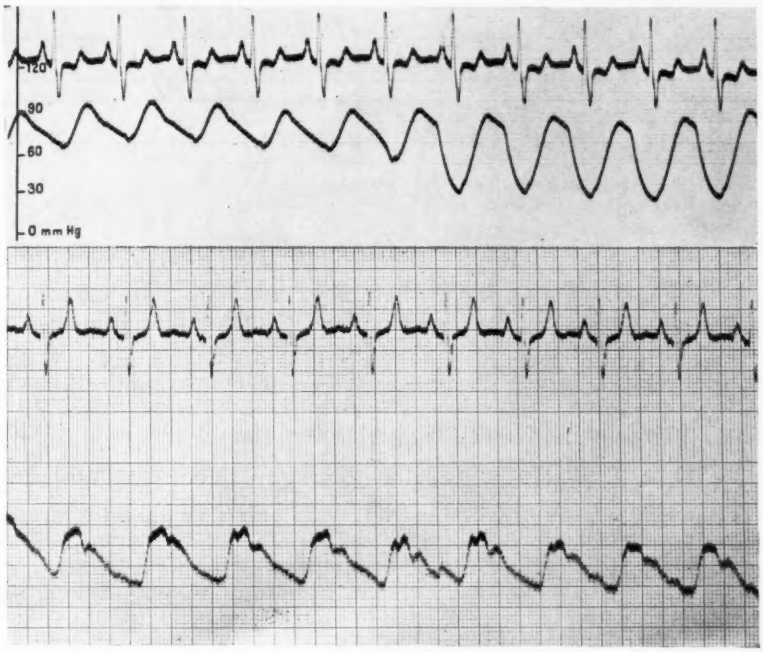

FIG. 9.—Eisenmenger's complex. The tracings have an arterial form and show premature closure of the semilunar valves. The pressures (above) are raised; the electrokymogram of the right main branch of the pulmonary artery (below) shows a systolic plateau.

In congenital heart disease with increased pulmonary flow (17 patients; 2 patent ductus and 15 atrial septal defects), the tracings are superimposable. There seems to be an inverse relation between the level of the pressure and the size of the pulsations. For a given flow a large kinetic pulsation corresponds to low pressures, and a reduced kinetic pulsation to raised pressures.

In the Eisenmenger complex, the two curves are again apparently analogous and are characterized by the existence of a plateau extending from systole into diastole.

The comparative study of the electrokymogram and pressure curves registered at the level of the pulmonary arterial tree appears to be of interest. Such a study allows a precision of diagnosis of the site of pulmonary stenosis and also, without any doubt, allows an estimation of the flow, both in cases of persistent ductus arteriosus and atrial septal defect.

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THE BALLISTOCARDIOGRAM IN MITRAL VALVULAR DISEASE

BY

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In 1940 Starr reported several cases of rheumatic heart disease in which the ballistocardiogram showed an abnormal pattern; clinical improvement was associated with return of the pattern toward normal. Following this report, several authors found the ballistocardiogram abnormal in a high percentage of cases of rheumatic valvular disease. The changes noted were small I waves, notching and slurring of the I–J segments, tall L and N waves, and " bowing " of J–K segments. However, these changes were not considered as pathognomonic of specific types of valvular lesion. The first attempt to ascribe these changes to a specific valvular lesion was by Davis *et al.* (1953) who found in cases of " pure " mitral stenosis an additional wave preceding the normal I wave. They referred to this abnormality as " doubling " of the I wave. Dock *et al.* (1953) noted several characteristic alterations in the ballistocardiogram in cases of pure mitral stenosis. These included lack of respiratory variation of the J waves and an absence of increase of the J waves following exercise. Brown *et al.* (1952) observed tall N waves in several cases of mitral stenosis. In cases of mitral insufficiency, Kuo and Schnabel (1953) described an additional positive systolic deflection interposed between the I and J waves.

This study was undertaken to determine if characteristic changes in the ballistocardiogram do occur in cases of mitral stenosis and/or insufficiency. Furthermore, serial records were studied in a number of patients with mitral stenosis both before and after mitral valvotomy.

Material and Methods

The records were obtained from a high-frequency ballistocardiograph (Sanborn) following a four-hour fasting period, late in the morning.

Forty-four patients are included in this study, all of whom suffered from rheumatic mitral valvular disease, presumably inactive. The diagnosis was established according to the usual clinical, X-ray, electrocardiographic, and other laboratory data. In 31 of the 44 patients, cardiac catheterization was performed. In the patients who underwent valvotomy, serial ballistocardiograms were recorded before operation and during a period of from two months to one year following valvotomy.

The first group comprises 30 patients with predominant mitral stenosis (Table I) of whom 20 had successful valvotomy carried out by Mr. H. Milwidsky ; in two of them, a mild degree of insufficiency was detected at the time of valvotomy. In four others valvotomy was not attempted because extensive thrombosis in the left atrium was found at the time of operation. Of the six unoperated cases, there was no significant degree of incapacity in three and three were in advanced congestive heart failure.

The second group consists of fourteen patients with predominant mitral insufficiency With three exceptions (aged 16, 17, and 43 years) all were in the age group 20–40 years. All had some degree of incapacity, severe in 7 (4 with signs of congestive heart failure).

The ballistocardiograms were examined with regard to amplitude, shape, and time relations between the ballistic waves and the QRS complexes of the electrocardiogram and the intervals between the various ballistic waves were measured. An attempt was made to correlate the hæmodynamic data obtained by

* This study was carried out with the support of the Lown Fund.

cardiac catheterization with the various ballistic waves, such as (1) left and right atrial pressures to the G–H, M–N complexes; (2) pulmonary artery pressure, pulmonary vascular resistance, and right ventricular work on one hand, to the H–I–J complexes on the other hand; (3) cardiac output to the J waves; and (4) systemic vascular resistance and peripheral arterial pressures to the J–K complexes.

TABLE I

CLINICAL FEATURES OF CASES OF MITRAL STENOSIS

Patient No.	Age	Sex	Degree of incapacity	Congestive heart failure: Before valvotomy	After valvotomy	Diagnosis
1	29	F	+++	+	+	Stenosis
2	27	M	++	+	0	Stenosis
3	44	F	++++	++	0	Stenosis
4	22	F	++	0	0	Stenosis
5	31	M	++	+	0	Stenosis
6	21	F	++	+	0	Stenosis
7	38	F	++	+	+	Stenosis
8	22	F	++	0	0	Stenosis
9	23	F	++	+	0	Stenosis
10	23	F	++	+	0	Stenosis
11	31	F	++	+	0	Stenosis
12	40	F	++++	+++	0	Stenosis
13	30	M	++	0	0	Stenosis
14	32	F	++++	++	0	Stenosis
15	19	M	++	0	0	Stenosis
16	31	F	++	+	0	Stenosis
17	19	M	++++	++	0	Stenosis
18	22	M	++	0	0	Stenosis
19	33	F	+++	+	+	Sten. and Ins.
20	17	F	++	0	0	Sten. and Ins.
21	42	M	++	0	No valvotomy	Stenosis
22	47	F	++	0	No valvotomy	Stenosis
23	22	M	+	0	No valvotomy	Stenosis
24	40	F	++++	++	No valvotomy	Stenosis
25	19	F	+	0	No operation	Stenosis
26	25	F	+	0	No operation	Stenosis
27	16	F	+	0	No operation	Stenosis
28	45	F	+++	+	No operation	Stenosis
29	26	F	++	+	No operation	Stenosis
30	44	F	+++	++	No operation	Stenosis

RESULTS

Time Relations between Ballisto- and Electrocardiographic Deflections. The time intervals between the Q waves and the I waves of the ballistocardiogram were found to be fairly constant, regardless of whether stenosis or insufficiency was present, and varied from 0·15 to 0·17 second. The time intervals between the I and K waves were also fairly constant and varied from 0·14 to 0·18 second. These slight variations in the intervals were apparently due to the differences in the pulse rate.

Correlation between the Hæmodynamics of the Right Heart and the H–I Complexes. Of 30 patients with mitral stenosis, comprising the first group, cardiac catheterization was performed in 27: in 16 of these pulmonary artery pressure and pulmonary vascular resistance were found to be much increased, more than 60/30 mm. Hg and 600 dyn./cm.$^{-5}$/sec. respectively. In 10 out of these 16 cases the H waves were much enlarged and in most of them peaked. In the remaining 6 the H waves were slurred and small or iso-electric. In the 11 in which the pulmonary artery pressure and the pulmonary vascular resistance were normal or moderately raised (up to 50/20 mm. Hg and 400 dyn./cm.$^{-5}$/sec. respectively), the H waves appeared normal in nine and enlarged in one. Ballistocardiograms after operation showed a gradual change of the enlarged H waves toward normal.

In 4 of the 14 patients suffering from predominant mitral insufficiency, the pulmonary artery pressures and pulmonary vascular resistances were measured and were found to be raised in three. In two of the latter the H waves were enlarged while in the other two they were normal.

Cardiac Output and J Waves. Cardiac output was calculated according to the Fick principle in 31 cases. No correlation was found between the cardiac output and the size of the J waves. In most cases the J waves were small but of normal shape prior to operation. In cases where the J waves were small, a significant increase of the I–J stroke was observed after successful valvotomy.

Peripheral Arterial Pressure, Systemic Vascular Resistance, and K Waves. The K waves of the ballistocardiogram tended to be deep in most of the cases, regardless of the height of the peripheral arterial pressure and systemic vascular resistance, and did not change significantly after valvotomy.

L, M, N Waves. Tall N waves were found in three of the twelve cases with pure mitral stenosis without congestive heart failure. Of the ten cases with predominant mitral insufficiency without congestive heart failure, one showed tall N waves. Tall L and N waves were found in 16 out of the 22 patients with congestive heart failure, whether the underlying condition was predominant mitral stenosis or insufficiency.

General Appearance of the Ballistocardiogram. There was a good correlation between the clinical picture (subjective complaints, degree of incapacity, right-heart enlargement, degree of pulmonary congestion, etc.) and the pattern of the ballistocardiogram. Prior to valvotomy the ballistic pattern was irregular, the respiratory variations were marked, and the interrelation of the various waves disproportional. Following valvotomy the J waves appeared abnormal and were slurred or notched for a period of about three months; thereafter where the clinical and laboratory data suggested improvement a gradual return of the ballistic pattern to normal occurred. This change in the ballistic pattern was especially evident with regard to the H–I–J–K complexes. Table II summarizes the results obtained by cardiac catheterization in 17 of the 18 patients who underwent valvotomy; Fig. 1 shows a schematic drawing of the ballistocardiograms before and after valvotomy. Fig. 2 illustrates serial records obtained in Case 3 before and after valvotomy.

Discussion

This study was undertaken to evaluate the aid offered by the ballistocardiogram in the differential diagnosis between predominant mitral stenosis and predominant mitral insufficiency, and in the

TABLE II

Hæmodynamic Data in 17 Patients with Mitral Stenosis who underwent Valvotomy

Patient No.	Pulmonary artery pressure (mm. Hg)	Pulmonary vascular resistance (dyn./cm.$^{-5}$/sec.)	Systemic arterial pressure (mm. Hg)	Systemic vascular resistance (dyn./cm.$^{-5}$/sec.)	Cardiac output (l./min.)	R.V. work (kg./min.)
1	24/9	261	100/85	1429	5·2	1·20
2.	32/13	267	120/90	1025	7·8	1·70
3	75/40	1001	105/75	1345	5·1	3·57
4	98/	1273	110/70	2575	2·7	1·58
5	No catheterization performed					
6	42/15	593	100/75	1822	3·6	0·67
7	76/13	1146	120/85	2019	3·8	1·33
10	70/50	1850	85/65	2220	2·7	2·87
11	50/35	405	90/70	940	7·5	4·26
13	42/23	688	105/80	2021	3·5	1·41
14	102/48	1475	103/61	2360	2·7	1·84
15	83/39	815	115/70	1028	5·9	4·81
16	62/27	790	105/70	1720	4·1	2·55
17	121/50	2005	110/80	2360	3·4	3·93
18	88/45	1009	105/65	1555	4·0	2·72

The serial numbers correspond to those in Table I.

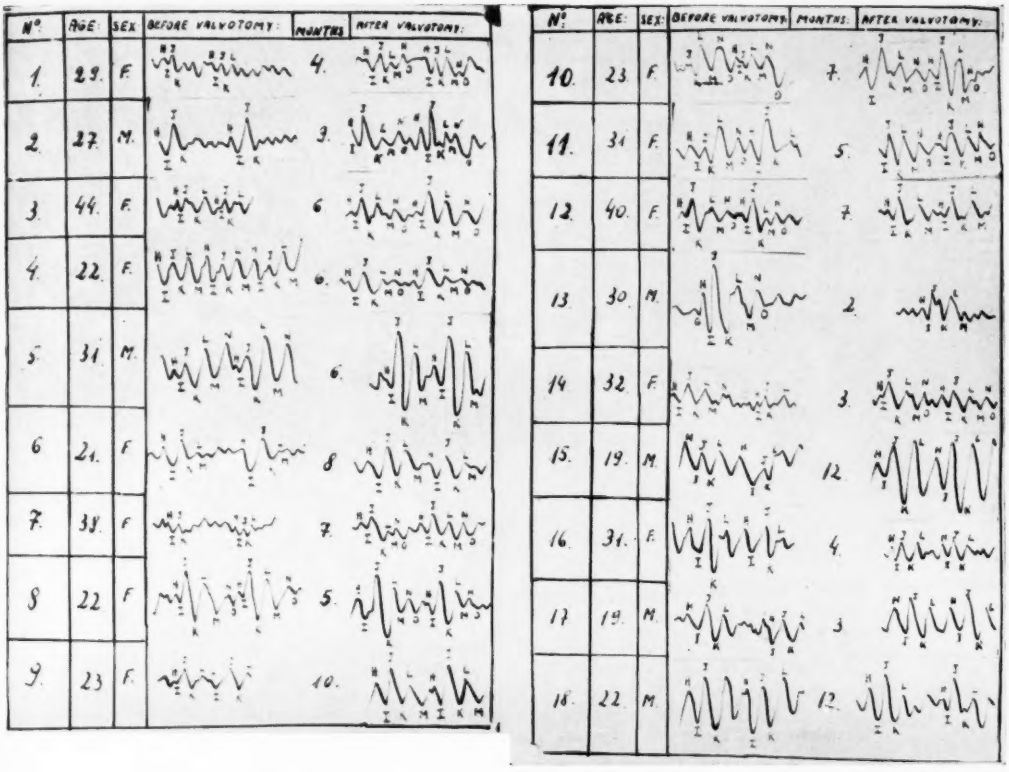

FIG. 1.—Schematic drawings of ballistocardiograms obtained before and after valvotomy. The serial numbers correspond to those in Tables I and II.

evaluation of the hæmodynamic alterations occurring in patients undergoing valvotomy. The reports of Davis *et al.* (1953) and Kuo *et al.* (1953) suggest that the ballistic pattern may be of value in differentiating patients with stenosis from those with predominant mitral insufficiency. However, in our series none of the previously described abnormalities such as " doubling " of the I wave, or the interposed upward deflection between I and J were found to be characteristic for either mitral stenosis or insufficiency. Tall L and N waves were found fairly regularly in cases of congestive heart failure, whether due to mitral stenosis or to mitral insufficiency. It appears to us, therefore, that the ballistocardiogram is of no value for differentiating between mitral stenosis and insufficiency. Non-specific changes such as marked respiratory variations, irregular pattern, and small J waves were present in a high percentage of patients with either mitral stenosis or insufficiency.

Follow-up ballistocardiograms after valvotomy showed return toward normal of the exaggerated respiratory variations and of the irregular pattern present before operation. The notching and slurring of the J waves found immediately following operation, which probably indicated myocardial damage due to the surgical procedure, disappeared within about three months and the I–J stroke became normal. These observations indicate that the ballistocardiogram may be a reliable method of evaluating hæmodynamic alterations after valvotomy (Reissman *et al.*, 1953).

An attempt was made to correlate the various hæmodynamic data obtained by cardiac catheterization with the various ballistic waves. The small number of cases with extreme pulmonary

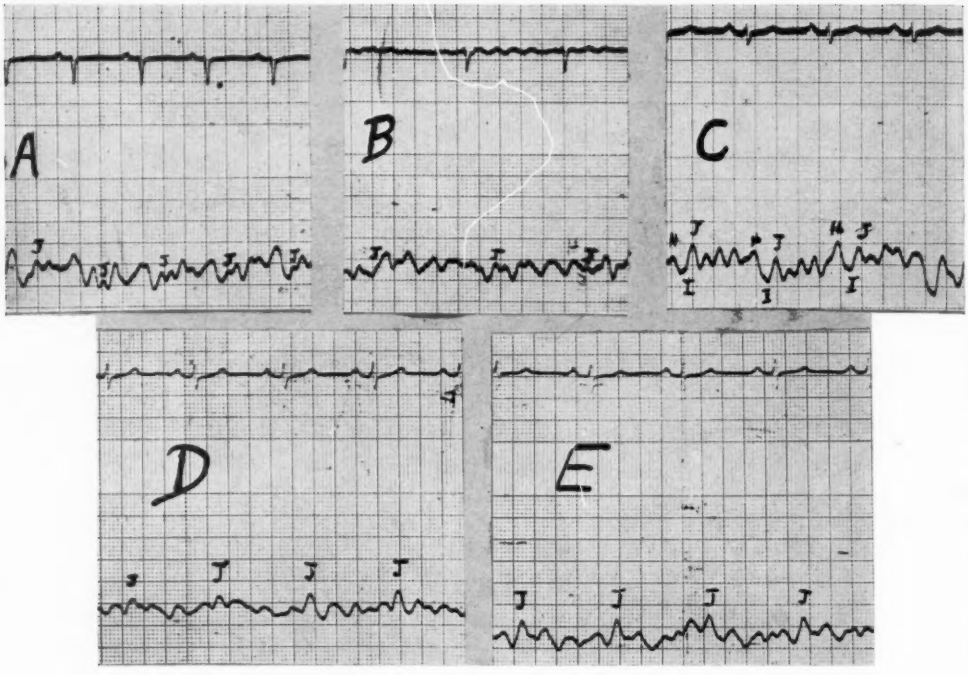

FIG. 2.—Serial ballistocardiographic records from a patient with tight mitral stenosis before (A) and following valvotomy (B–E). The last record (E), was taken five months after operation.

hypertension, in which the H–I complexes were much enlarged, are too few to indicate significant correlation. No correlation was found between the cardiac output and the size of the J waves. Neither was there any parallelism between the peripheral blood pressure or peripheral systemic vascular resistance and the size of the K waves.

SUMMARY

The ballistocardiogram was recorded in 44 patients with rheumatic valvular disease, mitral stenosis, and mitral insufficiency. In 18 of these, mitral valvotomy was successfully performed and serial ballistocardiograms were recorded at monthly intervals.

The ballistocardiogram did not reveal any specific pattern either for mitral stenosis or for mitral insufficiency.

No correlation could be established between the hæmodynamic data obtained by cardiac catheterization and the changes found in the ballistocardiogram. The ballistocardiogram was, however, thought to be a useful index for evaluating clinical improvement after successful valvotomy.

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THE INFLUENCE OF AGE ON THE HÆMOGLOBIN LEVEL IN CONGENITAL HEART DISEASE

BY

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The hæmoglobin content of the blood is a convenient out-patient test, and it has some value in the assessment of cyanotic heart cases both before and after operation (Campbell and Deuchar, 1953 and Campbell, Deuchar, and Brock, 1954). However, the theoretical background to variations of the hæmoglobin level in congenital heart disease is not well understood.

When the oxygen tension of arterial blood is reduced by altitude, it is comparatively easy to demonstrate an inverse relationship between oxygen tension and hæmoglobin level (Fitzgerald, 1913; Hurtado *et al.*, 1945), but in congenital heart disease the relationship is less obvious. This has variously been attributed to the presence of a severe associated disease (Talbot *et al.*, 1941), to a relative deficiency of iron (Brinton, 1951), and to the complicating effect of possible changes in circulatory flow (Holling, 1952). Little attention has so far been focused on the effect of age of the patient, although it is clear that most high altitude studies have been conducted on homogeneous populations of adults, while the congenital heart series have always included a large and rather varied proportion of children. It was therefore thought of interest to examine data from a large group of congenital heart patients, acyanotic as well as cyanotic, in order to determine the influence of age.

METHODS

Collection of Blood Samples. The sampling errors introduced by prolonged venous or capillary stasis have been discussed by Peterson *et al.* (1943). For the present purpose, blood samples were collected directly from the right side of the heart and from the femoral artery during the course of cardiac catheterization. Samples were kept in syringes at 0° C. for a maximum of 2–3 hours. The syringes were lubricated with silicone and contained a trace of heparin and one drop of mercury. Prior to analysis the syringes were shaken for 1–2 minutes to allow mixing and warming to room temperature, and then the contents were transferred anaerobically to Ostwald pipettes. Five or six independent samples were obtained from each subject.

Method of Analysis. The percentage saturation and total oxygen capacity of the samples were estimated by the Haldane blood gas analysis apparatus (Douglas and Priestley, 1948). The repeatability of measurements by this technique is quite good, the oxygen uptake in any one estimate usually differing by no more than 0·001 ml. from the mean value, and the oxygen capacity rarely differing by more than 0·005 ml. from the mean value (Ernsting and Shephard, 1951). The original technique, using bicarbonate buffers, gave values for oxygen capacity that were 5–7 per cent lower than those obtained by the Van Slyke apparatus (Bierring *et al.*, 1937), this error arising largely from oxidation of the lipoid fraction of the plasma (Litarczek, 1928). However, it has now been shown that if borate buffer of *p*H10 be used in place of the bicarbonate buffer, there is no systematic difference between the Haldane and Van Slyke methods (Courtice and Douglas, 1947).

The Subjects. The patients taking part in this investigation were 350 unselected cases of congenital heart disease—166 acyanotic, and 184 cyanotic. Their ages ranged from 2–60. Patients under the age of 6 were invariably under light pentothal anæsthesia, and some patients in the 7- and 8-year age groups were also given a general anæsthetic. Pentothal was originally selected as the anæsthetic agent because it was

believed that this would not affect the blood gas estimations; there has been one report suggesting that in dogs, pentothal produces some hæmodilution (Penrod and Hegnauer, 1948), but in the present series there was no difference between anæsthetized and conscious children of a comparable age group.

Analysis of Results

Patients were divided into two broad groups, the cyanotic and the acyanotic, on the basis of arterial oxygen saturation. The dividing line (breathing air) was taken as 94 per cent in the conscious and 92 per cent in the anæsthetized patients.

Having divided the patients in this way, the acyanotic patients should give some indication of the influence of cardiac disease on hæmoglobin production, uncomplicated by the effects of changes in arterial oxygen tension. To facilitate this analysis, cases were grouped according to age, as shown in Table I. Up to the age of 15, there was little difference between the sexes, and they have not therefore been distinguished. Over the age of 15, the women patients showed a slightly lower hæmoglobin level than the men, the difference being statistically significant in the 19·5–29·5-years age group.

TABLE I
Hæmoglobin Level at Different Ages
(Mean and standard error)

Age	Acyanotic patients		Cyanotic patients
2·5—4·5	12·9±0·4 ml. O_2/100 ml.		21·7±2·4 ml. O_2/100 ml.
4·5—5·5	13·9±0·4		21·0±2·0
5·5—6·5	14·5±0·8		22·7±1·3
6·5—7·5	15·0±0·6		21·4±1·6
7·5—8·5	15·1±0·7		23·1±1·3
8·5—9·5	15·5±0·6		23·7±1·2
9·5—10·5	15·9±0·9		25·4±2·8
10·5—11·5	16·1±0·6		25·2±1·9
11·5—12·5	16·0±0·4		24·3±1·4
12·5—13·5	16·8±0·4		25·2±2·0
13·5—14·5	17·2±0·5		25·8±1·6
14·5—15·5	18·6±0·5		23·3±2·4
	Men	Women	
15·5—19·5	17·4±0·5	16·6±0·7	25·6±1·1
19·5—29·5	17·9±0·5	16·1±0·6	24·0±0·9
29·5—39·5	17·7±0·3	17·3±0·5	21·5±0·8
39·5—49·5	17·2	17·3±1·0	17·3±1·5
over 49·5			17·5

Does the hæmoglobin/age curve for the acyanotic group of patients differ significantly from normal? Owing to the specialized nature of the cardiac clinic, the patients did not conform to the classical "hospital" sample, but were drawn from a wide area of the country and included all social grades. The figures are therefore best compared with values from the M.R.C. survey (1945), which covered a similar wide cross-section of society. It will be noted (Fig. 1) that the curve for the present group of subjects is set at a lower level than the M.R.C. curve. A further significant feature is the steeper slope shown by the congenital heart cases. There are various possible explanations for these differences but they may well represent a genuine effect of cardiac disease. Many acyanotic patients, particularly the young children, are below average weight, and it seems quite probable that this poor general nutrition is reflected also by a rather low hæmoglobin content of the blood.

Having established a normal hæmoglobin curve for acyanotic congenital heart cases, it is possible to consider how this curve is modified at different ages by the added factor of a reduced arterial oxygen tension. It can be seen (Fig. 2) that the mean curve for the cyanotic patients lies at a much higher level. Like the acyanotic curve it climbs progressively throughout childhood.

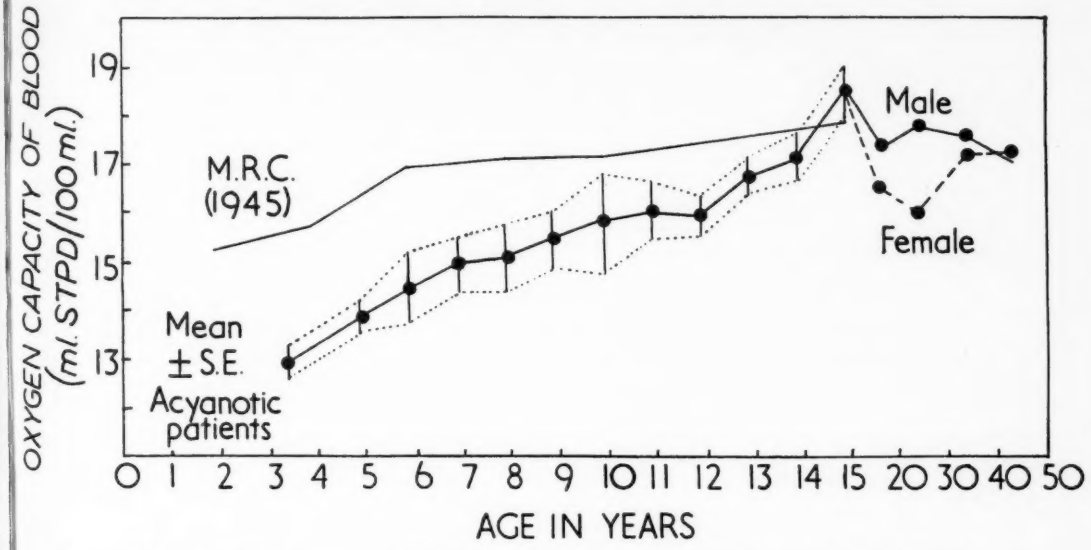

FIG. 1.—The relationship between age and hæmoglobin level (166 cases of acyanotic congenital heart disease). The mean curve (with standard error) is compared with a curve for normal children (M.R.C., 1945).

However, beyond the age of 20, the curve falls away rapidly, and in the 40–50 age group there is little difference between acyanotic and cyanotic hæmoglobin levels. This anomaly may be explained by the death of an increasing proportion of the severe cases. Thus only the less severely affected patients with a relatively normal hæmoglobin contribute to the curve during later adult life.

The possibility of distinguishing acyanotic from cyanotic patients on the hæmoglobin level alone is also examined in Fig. 2. To the mean curve for acyanotic cases has been added an area corresponding to twice the standard deviation of a single observation at a given age. This gives an upper limit of normality that will only be transgressed by one patient in twenty, and it is reasonable to suspect patients with a hæmoglobin level greater than this as having a right-to-left shunt. It is important to note that in children under the age of 5, the upper limit of normal oxygen capacity is as low as 15 ml./100 ml. (under 75% hæmoglobin). How many cases with slight cyanosis have a hæmoglobin below the upper limit of normality? It is not possible to answer this question from the standard deviation of the cyanotic curve, since the hæmoglobin level of cyanotic patients shows a skewed distribution, a limiting hæmoglobin level being reached with increasing severity of the heart disease (Brinton, 1951). However, it is possible to indicate on Fig. 2 those of the 184 cyanotic cases that have a hæmoglobin level within normal limits. The percentage at different ages is summarized in Table 2. It would seem that during childhood some 85 per cent of "cyanotic" patients can be recognized purely on hæmoglobin level, but in adult life there is an increasing tendency for the hæmoglobin to fall within normal limits.

DISCUSSION

It seems clear from the present results that in children the proportion of cyanotic heart cases having an increased hæmoglobin level is sufficient to make this a useful clinical test of a right-to-left shunt. However, if the hæmoglobin level is to be used in this way, it is essential to note both the normal age variation and the general effects of cardiac disease on the hæmoglobin level.

It is well recognized that some degree of iron deficiency anæmia exists in a significant proportion

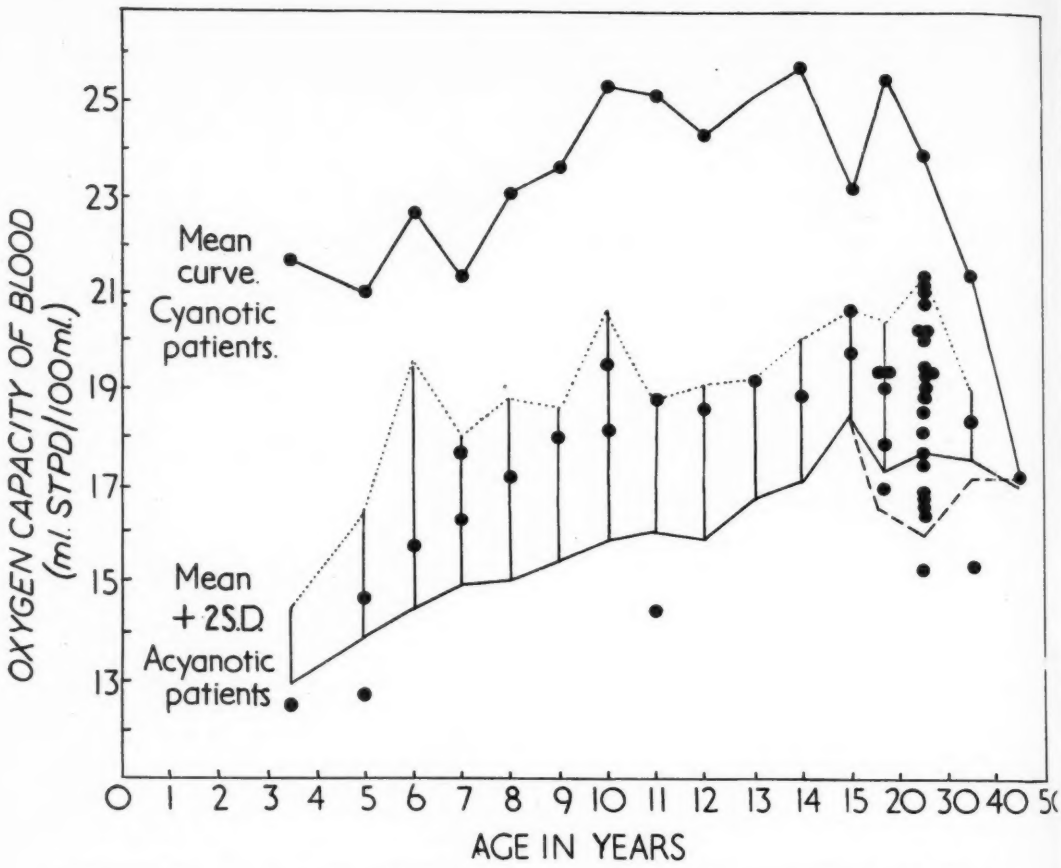

FIG. 2.—The effect of a reduced arterial oxygen tension on the hæmoglobin level in congenital heart disease. The normal limit (twice standard deviation) for acyanotic patients is compared with the mean curve for cyanotic patients. Individual cases of cyanotic heart disease having a hæmoglobin level falling within normal limits are marked on the graph (total number of cyanotic patients 184).

TABLE II

PERCENTAGE OF CYANOTIC PATIENTS WITH HÆMOGLOBIN LEVEL WITHIN NORMAL LIMITS AT DIFFERENT AGES

Age group	Number of cases	Percentage with normal hæmoglobin
2·5—6·5	24	16·7
6·5—9·5	23	16·9
9·5—12·5	23	21·7
12·5—15·5	19	21·1
15·5—19·5	25	20·0
19·5—39·5	58	39·6

of otherwise healthy children (Mackay *et al.*, 1946), but it is not altogether clear whether the incidence of this type of anæmia is increased in the presence of congenital heart disease. However, it is known that many congenital heart cases, acyanotic as well as cyanotic, have a weight that is below average, particularly over the period when parental restriction limits their activity. The present curve for the acyanotic cases lends support to the view that hæmoglobin formation is also inadequate, especially in young children, and such cases might well benefit from iron therapy.

If iron intake falls below requirements in acyanotic cases, the deficiency in the cyanotic is considerably greater, since in this group poor general nutrition is more common, and the iron requirement is much increased by the polycythæmia. Nelson *et al.* (1947) have pointed out that an improvement in hæmoglobin level can sometimes be brought about by bed rest alone, and it would seem that some other factor—perhaps oxygen lack—is also restricting hæmoglobin formation in the more severe forms of cyanotic heart disease. However, it has been demonstrated (Brinton, 1951) that where the increase of hæmoglobin formation has not kept pace with the polycythæmia, improvement can be achieved by systematic iron therapy without further restriction of a patient's activity, and in cases of this type it would appear beneficial to persist with iron therapy until no further increase of hæmoglobin level can be detected.

The normal red cell count does not vary greatly with age (Moncrieff and Evans, 1953), and is little influenced by the various factors that appear to restrict hæmoglobin formation in congenital heart disease. The relationship between arterial oxygen tension and red cell count therefore remains fairly straightforward, and it is easy to understand why earlier authors found these two variables yielded a better correlation than arterial oxygen tension and hæmoglobin level in cases of congenital heart disease.

Summary

The relationship between age and hæmoglobin level has been studied in 350 cases of congenital heart disease. The acyanotic cases showed a hæmoglobin level rather lower than previously reported normal values, particularly in the early years of childhood. The mean curve for the cyanotic cases was far above the acyanotic curve throughout childhood, and up to the age of 20 some 85 per cent of cyanotic patients could be distinguished from the acyanotic by estimation of the hæmoglobin level alone. In adult life the hæmoglobin curve for the cyanotic patients gradually merged into the acyanotic curve, perhaps owing to the death of the more severe cyanotic cases.

The rather poor correlation between arterial oxygen tension and hæmoglobin level in cyanotic heart disease is probably due partly to variations of hæmoglobin level with age, and partly to factors restricting hæmoglobin formation in the more severe cases.

The patients forming the basis of this study were under the clinical care of Dr. Campbell, and I am grateful to him for allowing me free access to his records. Nearly 2000 Haldane blood gas analyses were carried out, and it is a pleasure to acknowledge the help given by other members of the Cardiac Department with this work.

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MYOCARDIAL TOXOPLASMOSIS

BY

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In an earlier article we reported (Paulley *et al.*, 1954) a series of cases with myocarditis believed to have been caused by toxoplasma infection. In this paper the cases previously described are again presented with the addition of photographs, photomicrographs, and electrocardiographic tracings. More details of the necropsies are included, and there are more data concerning other members of the patients' families. A further case probably of the same nature is recorded.

Pseudocysts of toxoplasmosis have been observed several times in the heart muscle of patients dying of the acute generalized acquired variety of the disease (Pinkerton and Weinman, 1940; Pinkerton and Henderson, 1941; Nery Guimarães, 1943; Kass *et al.*, 1952; Sexton *et al.* (quoted by Kass, 1952); and Prior *et al.*, 1953). In most cases evidence of the infection has also been found in the brain, spleen, liver, and lungs. In the hearts of these acute cases focal necrosis is the common finding. Electrocardiography was carried out in two instances before death. Bengtsson (1950) appears to have been the first to report myocarditis as a presenting feature of toxoplasmosis, although here again it was part of the usual clinical picture of the acute acquired disease. It provided a further example of the liability of laboratory workers to this infection, and on this occasion the oral route was the probable avenue of infection. After a long convalescence recovery took place.

Our observation occurred in the following way. A young man presented in 1954 with an unexplained severe myocarditis, and some signs suggestive of meningo-encephalitis. Eventually a speculative diagnosis of toxoplasmosis was advanced and the serum was examined through the courtesy of Dr. Cathie. The complement fixation test was strongly positive. It was realized that this might be a chance finding, until a fortnight later another patient of 39 with unexplained myocarditis was also found to have a positive test. A thorough investigation was then made of these two patients' families, with startling results not only in the number of positive complement fixation tests, but also in the findings of quite unsuspected symptomless heart disease in young siblings, and in one of the families a striking tale of sudden death or heart failure in a mother of 39, a brother of 16, and a sister of 20. A third patient, aged 24, was then found, symptom free, who had been medically rejected for Sandhurst because of a large heart at the age of 19; he, too, had strongly positive serological tests.

Positive complement fixation tests may be expected in 5 per cent of the population in North-West England (Macdonald, 1950) and in Cathie and Dudgeon's series (1953) the figure is given as 7 per cent. The frequency of positive tests in our cases and their close relatives provided most powerful circumstantial evidence that in fact toxoplasmosis was the cause of the myocarditis.

Ultimate and absolute proof was, however, lacking. We had been unable to find pseudocysts in the only heart of our series available for microscopic examination. An attempt to grow toxoplasmas by mouse inoculation with a suspension of finely ground heart muscle from one of our patients, who died a few months ago, failed. But very recently Cathie has reported (1955) successful isolation of toxoplasmas by mouse inoculation from the heart muscle of a patient of Dr. Alun

Williams of Middlesborough who died of an obscure myocarditis and in whom the serological tests had been found positive six weeks previously (C.F.T. 1/8; dye test 1/32). This was most important confirmatory evidence for our thesis which had previously relied on serological tests and a certain degree of probability.

Case Reports

Case 1. A man, aged 24, was admitted to the East Suffolk and Ipswich Hospital on Sept. 20, 1953. He had a large left pleural effusion, low grade fever, a large heart (Fig. 1), and residual signs of a stroke affecting the right side which had occurred a week before he came in. He was treated with penicillin and streptomycin and was discharged a month later, only to be readmitted on February 19, 1954, with cardiac failure. Electrocardiograms showed auricular fibrillation and severe left bundle-branch block (Fig. 3). There was fever and mental confusion and left hemiplegia. He was reviewed at a clinical meeting, and among others the diagnosis of toxoplasmosis was considered.

Fig. 1.—Case 1. Teleradiogram of heart, January, 1954.

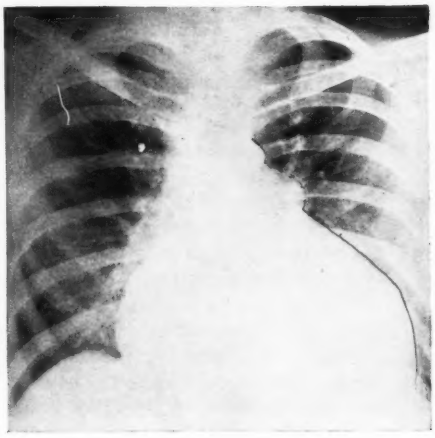

Fig. 2.—Case 2. Teleradiogram of heart, May, 1954.

Dr. I. A. B. Cathie tested the patient's serum for toxoplasmosis and found that the dye test was positive at 1/64, and the complement fixation test at 1/16. The patient's skull was radiographed, but no cerebral calcification was found. Efforts were then made to obtain further details of his family history. The patient's condition deteriorated gradually, and he died on Dec. 10, 1954.

Necropsy Report. Scalp, skull, and meninges were normal. The arteries at the base of the brain showed no evidence of disease. In the right cerebral hemisphere there was extensive old cystic softening of the lenticular nucleus, yellowish in colour and largely replaced by clear fluid. Its appearances were consistent with a duration of about one year. The remainder of the brain showed no naked-eye change and in particular there was no evidence of any calcification.

The heart weighed 960 grammes. The coronary arteries were of medium calibre and showed no evidence of atheroma. The myocardium everywhere showed extensive yellowish mottling or fibrosis. This was most marked at the apex where the consistence of the muscle was exceedingly dense and where there was a small amount of intramural thrombus formation. There was no evidence of any intra-auricular thrombus formation. The valves were normal (Fig. 4).

The liver weighed 1650 grammes. Its cut surface showed an appearance of very advanced nutmeg change.

Histological Examination. Sections of five portions of heart from different areas all showed substantially the same changes (Fig. 6 and 7).

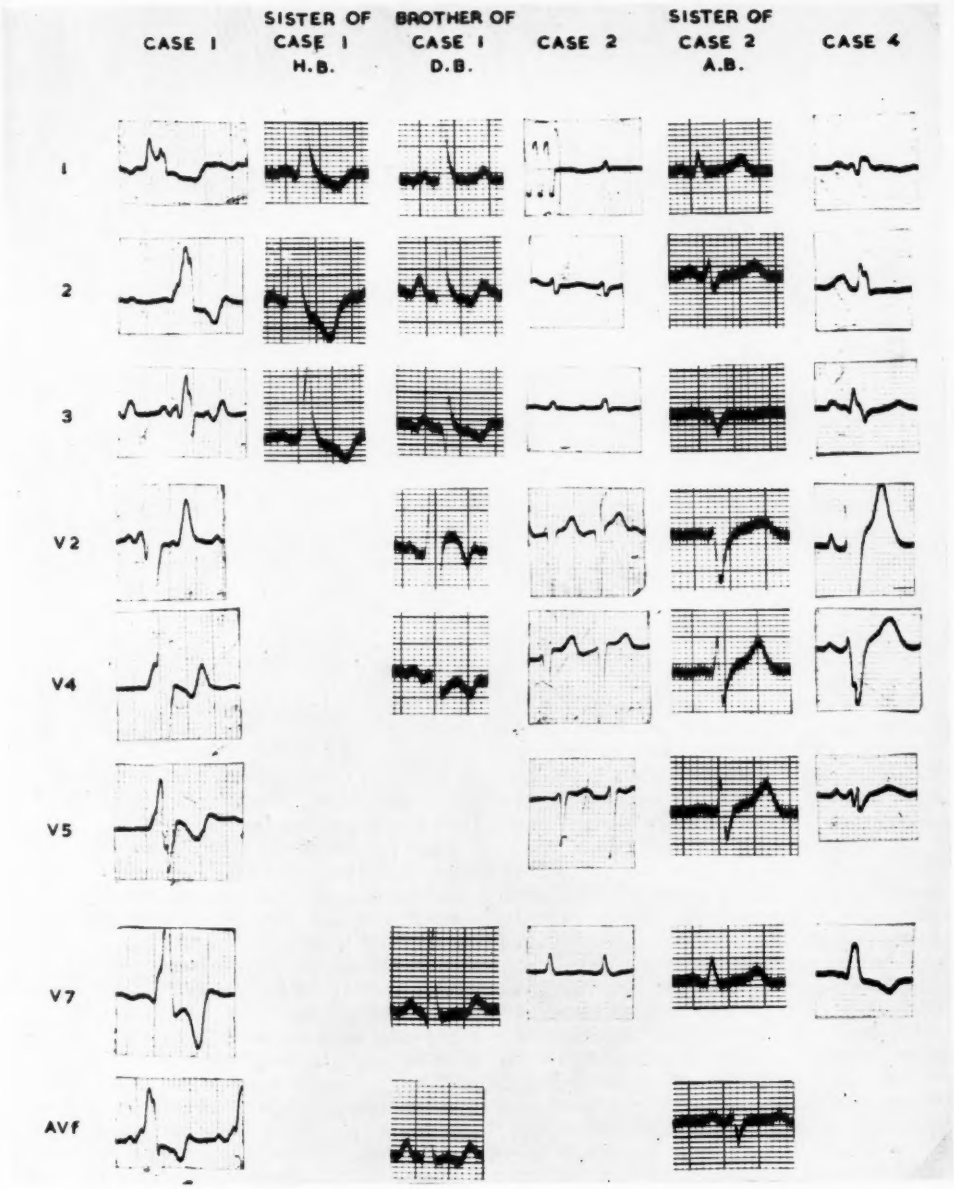

FIG. 3.—A series of electrocardiograms from Cases 1, 2, and 4, and some of their relatives.

FIG. 4.—The heart of Case 1, showing hypertrophied muscle, fibrosis, and intraventricular thrombus. Scale in inches.

1. Hypertrophied irregular muscle fibres (this change was less marked in areas with less fibrosis).
2. Generalized fine interstitial fibrosis varying from slight to moderate in degree.
3. Extensive areas of coarse fibrosis surrounding isolated hypertrophied myocardial fibres and often surrounding or adjoining tracts of necrotic-looking fibres.
4. No significant degree of active inflammatory cell infiltration and no evidence of pseudocysts or other indication of active toxoplasmosis.

Sections of pons and medulla showed no abnormality. The area of softening in the lenticular nucleus showed no specific changes and in particular appearances rather suggestive of miliary granulomata or pseudocysts were seen in the adjoining brain tissue.

Family History. The patient's mother died suddenly at the age of 39 in 1944. At necropsy the body was that of a well nourished woman. The legs were œdematous and the abdomen prominent. The brain showed an embolic necrosis in the left parietal lobe. The air passages contained frothy sputum. The lungs were large, firm, and slightly œdematous. The heart was very large (550 g.). All cavities were hypertrophied and dilated. The valves were normal and the coronary arteries healthy. There was ante-mortem clot in the left auricular appendage. The left ventricle was fibrotic. The liver was large and showed extensive chronic venous congestion. The spleen was firm and showed approximately three-fold enlargement. The kidneys were normal. The pelvic organs and intestines were normal. Death was due to congestive heart failure, myocardial fibrosis, and hypertension. Histological appearances were not recorded.

The father, upset by the mother's death and the responsibilities of his family, went into a mental hospital in 1945 and is still there. His heart is clinically normal. The complement-fixation test was anticomplementary, but the dye test was positive at 1/4. A brother of the patient died suddenly at the age of 16 in 1947 in a children's home. He is said to have had "meningitis" at the age of 3 years and to have had epileptic fits afterwards. A coroner's inquest and necropsy attributed death to heart failure from paroxysmal tachycardia, from which he is said to have suffered. His heart was generally enlarged at necropsy, and he had a large "fibrotic spleen." A second brother, aged 20, spends half his time in an institution and the other half "on the road." Since our first paper he has been traced and examined. There is no clinical evidence of heart disease, and his serological reactions and cardiogram and teleradiogram are all normal. A sister (twin of the second brother) died suddenly in June, 1954, in Whittington Hospital a few days after childbirth. She was admitted there in May, 1954, six months pregnant, and cardiac arrhythmia had been noted in the antenatal clinic. Œdema and albuminuria then developed, and she was thought to have

pregnancy toxæmia. The diagnosis was soon changed to congestive heart failure. There were no heart murmurs but many ectopic beats. Electrocardiography showed gross myocardial changes culminating in bundle-branch block (Fig. 3). She deteriorated despite treatment, and died with an embolism of the bifurcation of the aorta. At necropsy "myocarditis of unusual type" was found, the embolus arising from intracardiac thrombosis of the left auricle and ventricle (Fig. 5). Dr. J. D. O'D. Lavertine reported on the myocardium: "Severe cloudy swelling of hypertrophied fibres, slight fatty change, areas of dense young fibrous tissue, and diffuse fibrosis with focal non-specific chronic inflammation in myocardium of both ventricles, and with endocardial thrombosis. . . . The condition appears to be a non-specific myocarditis in the healing phase following severe focal necrosis." (Fig. 8). A third brother, aged 18, is in the army and

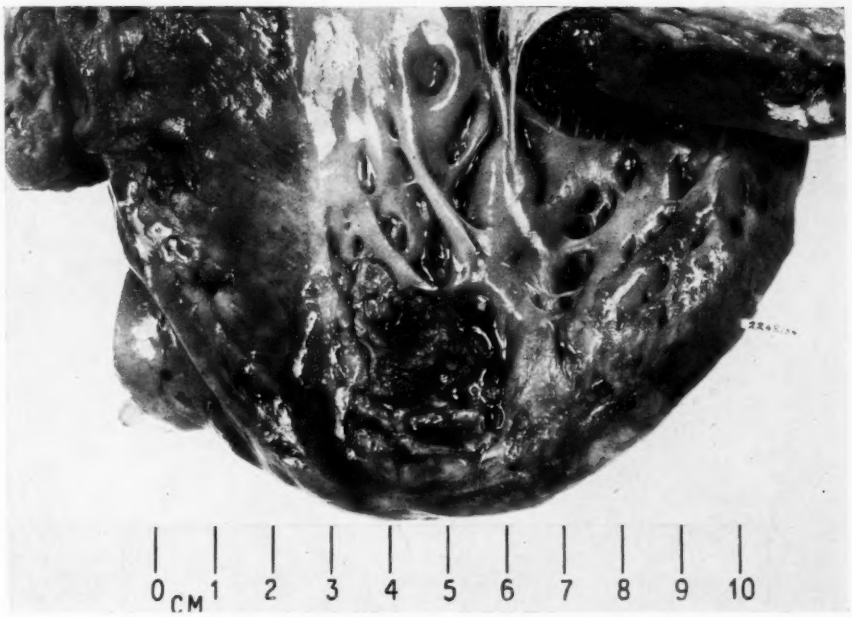

FIG. 5.—The heart of the sister of Case 1 (June S), shown for comparison.

doing well. He went to an approved school, and was not available for examination. A second sister, aged 15, has been in a children's home for ten years. Her I.Q. is 75 and electrocardiogram very abnormal, with wide QRS (0·12 sec). Radiographs of her chest and skull were normal. Her serum gave a positive result with the complement-fixation test at 1/16, and dye test at 1/32. A fourth brother, aged 13, has been in a children's home ten years. His I.Q. is 71, and electrocardiogram showed a prominent Q3, a small R wave in V1, a diphasic T in V1 and inverted T in V2 and V3, and slurring of S–T in V1–4. Radiologically his heart is of normal size. His serological findings have been negative.

Case 2. A man, aged 39, was admitted to hospital with dyspnœa on slight exertion and ankle œdema. Breathlessness had been gradually increasing for eight years. He had pain in his chest on hurrying. At the age of 17 he had had a "serious illness" described as jaundice and "gastric flu."

Examination revealed auricular fibrillation, a very large heart (Fig. 2), and a systolic murmur at the apex. Cardiogram showed complexes of very low voltage (Fig. 3). Because of our experience with Case 1 tests for toxoplasmosis were done, the dye test being positive at 1/32 and the complement-fixation test at 1/16.

The family history showed that his father was alive and well and that his mother died of cancer. A sister aged 37, was positive to the dye test at 1/16 and to the complement fixation test at 1/16. Another sister, aged 29, was negative to the dye test and the complement-fixation test. Radiography of her skull and chest

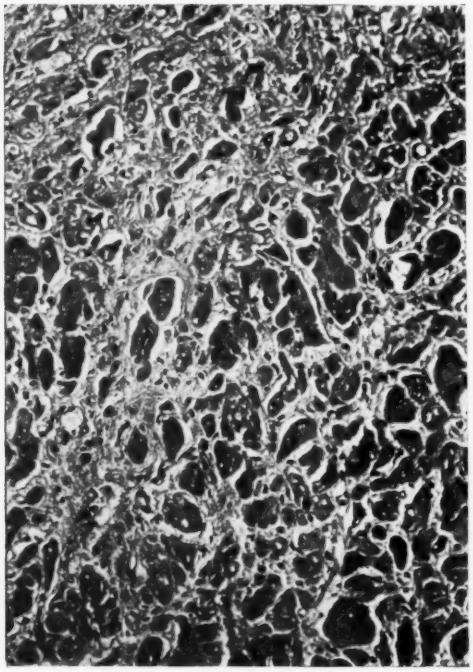

FIG. 6.—Case 1. Myocardium, showing diffuse fibrosis (×74).

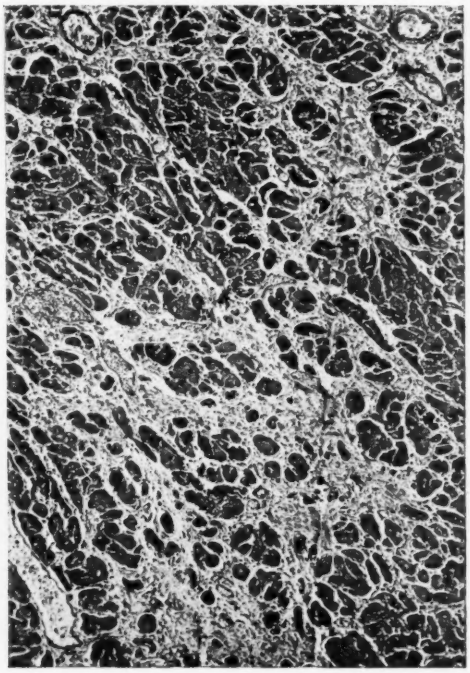

FIG. 7.—Case 1. Myocardium, showing diffuse fibrosis (×190).

was normal, and electrocardiography showed slight slurring of S–T segments. She was symptomless. A brother, aged 23, was positive to the dye test at 1/32, and to the complement-fixation test at 1/32. His heart was enlarged clinically and radiologically, his pulse was irregular, and electrocardiography showed auricular fibrillation. He was symptomless apart from much sweating on exertion. He had "german measles" twice, at the age of 11 and 19 years. Pets were always kept in this household, at one time as many as nine cats.

Case 3. A man, aged 24, was seen as an outpatient in June, 1954. He had no symptoms and played strenuous games, but had been rejected by a Service Medical Board at the age of 19 because of cardiomegaly, and a life assurance company had referred him for an opinion on his heart. He himself had had no serious illness.

On examination his heart was much enlarged. No heart murmurs were heard. Electrocardiographic findings were regarded as within normal limits. Because of our experience with the first two cases, serological tests for toxoplasmosis have been done, with the following results: dye test positive at 1/512 complement-fixation test positive at 1/32.

Case 4. An engineer's labourer, aged 43, complained in May, 1954, of a cough and frothy sputum waking him at night. He was diagnosed by his own doctor as having influenza, but he did not recover fully. In July, while on holiday, he noticed breathlessness on going up steps or when hurrying on the flat. In August he tried to return to work but had to give up after a week. He was admitted to hospital in December, 1954, for investigation. There was a history of pneumonia in 1943 and sciatica in 1952. He had otherwise been well and there was no history of recurrent winter cough. He had never had rheumatism.

Examination showed a small thin man, slightly cyanosed. A malar flush was present. There was no œdema. The pulse was 68 a minute and regular, the blood pressure 80/70. Gallop rhythm was present, but there were no murmurs. Fine râles were found at the lung bases. The liver was enlarged two finger-

breadths. He was regarded at once as "a very obscure case." The cardiogram showed right bundle-branch block, but no evidence of recent infarction (Fig. 3); after a test exercise there was no alteration in complexes to suggest ischæmia. Blood was then sent for toxoplasmosis tests; the C.F.T. was positive at 1/8 and dye test positive at 1/32. At the same time he was readmitted as an emergency with what turned out to be a thrombosis at the bifurcation of the aorta. He developed rapid auricular fibrillation terminally.

Necropsy Report. The heart weighed 520 grammes. The coronary arteries showed fairly extensive atheroma but were of wide calibre with no evidence of obstruction. Both ventricles were dilated; there was no pronounced thickening of their walls. The myocardium was very firm and of dense consistence; it showed generally a mottled appearance of coarse fibrosis; there was no evidence of any recent infarction. The valves were normal. There was no auricular thrombus formation.

The lower abdominal aorta showed fairly advanced atheroma. There was a large adherent thrombus completely occluding the lower 3 cm. and extending into the first few cm. of both common iliac arteries.

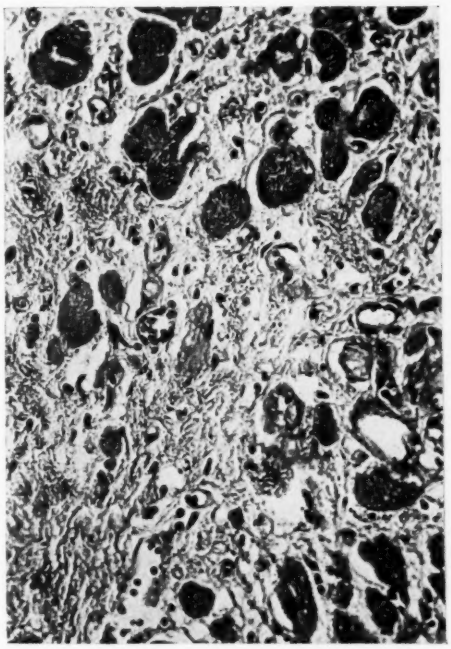

FIG. 8.—June S. Myocardium, showing necrotic muscle fibres (×310).

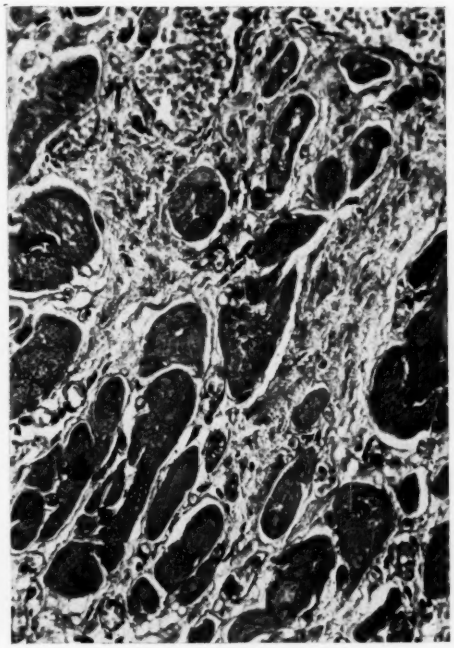

FIG. 9.—Case 4. Myocardium, showing fibrosis and hypertrophied muscle fibres (×310).

Histological examination of five pieces of the heart all showed extensive interstitial fibrosis. This was predominantly of loose acellular type. The distribution was fairly widespread although there were areas unaffected. The muscle fibres showed much hypertrophy. In the more severe areas of fibrosis they appeared degenerate—swollen and eosinophilic with loss of striation. No active inflammatory cell infiltration was seen and the process was obviously of long duration. Nothing was seen to suggest the presence of toxoplasma (Fig. 9).

Family History. After his death efforts were made to obtain details of his family history. His father died, aged 39. His mother had been ill with heart failure for a year before death at the age of 36 of dropsy. He was the youngest of four children. The eldest sister was interviewed and she said that she and the other brother and sister were well as far as she knew. Her blood was taken for toxoplasmosis tests and was

negative. The patient's wife and two children aged 7 and 9 also have normal findings in the serum. Teleradiograms of the chest and electrocardiograms were also carried out on the patient's family; they were considered to be within normal limits though there was slight doubt about the children's cardiograms and we intend to follow them futher.

Discussion

Since our previous communication more data have presented. The serological examination of June S's baby gave negative results; this was of interest as we expected them to be positive. However, there is no proof that the mother's blood was positive, though we believe it should have been. Also her twin brother returned from his wanderings, and in him full clinical examination, heart radiography, cardiography, and serum were normal. These findings are in the main against the infection in our cases being congenital, and this we had suspected previously because of the skipped sibling in the family of Case 2, and because of the 16 years separating Case 2 and his diseased younger brother. Necropsy of Case 1 revealed a heart almost identical macroscopically as well as microscopically with his sister's. Examination of the brain showed no evidence of encephalitis, but an area of softening of the right lenticulate nucleus was considered to be due to an old infarct.

Case 4 is of interest, as although his heart was large during life, at necropsy it did not show the gross hypertrophy of Case 1 or June S. This patient, rather older than the previous cases, was thought to have suffered a silent cardiac infarction and his bundle-branch block had been attributed to coronary disease until the positive serological test and necropsy. It is tempting to think that this is a common occurrence where unexplained heart failure is often attributed to previous hypertension, burnt out thyrotoxicosis, or coronary vascular degeneration with little evidence to support these diagnoses.

The consistent finding of cases in which the heart seems to be the organ predominantly affected could be explained by a specific strain of the organism with special affinity for heart muscle. Such a concept is perhaps not too extreme if one considers as parallels, leishmaniasis and trypanosomiasis, diseases caused by organisms comparable to toxoplasma, and displaying a variety of clinical features according to strain. A study of South American trypanosomiasis is particularly interesting in this respect, the organism having an undoubted predilection for heart muscle as well as brain and liver. Histologically, too, the appearances of the pseudocysts in Chaga's disease are somewhat similar to those of toxoplasma.

The questions of latency and chronicity remain undetermined. The fact that so many members of the families of Cases 1 and 2 are affected despite their ages being widely separated suggests latency though it is by no means proof of it. As is thought to happen in Chaga's disease there may be initial heart damage, and the subsequent healing may be partial or complete. If partial, the eventual heart failure is likely to be delayed many years. However, the presence of much necrosis of muscle fibres in the hearts of Case 1 and his sister June S. suggested recent activity, though we had every reason to suspect that their hearts had been infected many years before, because of the death of their mother in 1943 and a brother in 1947 apparently from the same condition.

The whole question of the serological tests and what they mean has been reopened by the recent Sheffield report (Beverley *et al.*, 1955) of a laboratory worker whose complement fixation test became negative within a few months of infection (Beattie, 1955): hitherto it had been thought that this did not happen. High, or rising titres in the dye test are essential for much reliance to be placed upon it, especially as it has now been shown that low titres can be caused by trichomonas vaginalis infection. In our own series, D.B., the younger brother of Case 1, had an electrocardiogram showing some evidence of anterior myocardial damage, but serological tests had been twice negative: clinically, however, he showed no sign of heart disease and his heart was of normal size. It is difficult to interpret this finding and to assess how much weight should be attached to it. At first sight the cardiograms of the children of Case 4 appeared abnormal, but

measurement and allowance for age has shown them to fall within physiological limits. We hope to follow the future of these three children, as there is an element of doubt.

It seems most important that every effort be made to isolate the toxoplasmas from heart muscle more frequently by mouse inoculation as Siim has done so successfully from lymph glands.

A possibility that has to be considered is that the toxoplasma infection in these myocarditis cases is incidental, and not primarily the cause of the heart damage. This presupposes that some situation had arisen in these patients which had encouraged a flare up of an earlier infection lying latent, or that they have become more liable to infection because of lowered resistance. We do not think that either of these theories is the probable explanation.

Despite the present uncertain position we suggest that toxoplasmosis should be suspected in all forms of obscure myocarditis, especially in familial cardiomegaly and idiopathic cardiac hypertrophy, and perhaps in some cases at present described as coronary disease in the young. Many of the histological changes in our cases could have been caused by long standing ischæmia, and though we found the large coronary vessels singularly free of disease in our patients, we have no evidence as to the state of the smaller branches.

Summary

Focal myocarditis due to toxoplasmosis has been recorded several times as part of the generalized acquired disease. Evidence is advanced that myocarditis may be the only presenting sequela of an earlier infection with toxoplasma, or a manifestation of an infection lying latent for a long time.

Details of four cases are recorded and of many members of their families who, though symptomless in the main, showed evidence of unsuspected heart disease on X-ray and electrocardiographic examinations.

A brother of Case 1 had an abnormal electrocardiogram but negative serology. The importance of this finding is discussed, especially in the light of the recent Sheffield patient in whom the complement fixation tests became negative within months of a known acquired toxoplasma infection.

A suggestion is made that there may be some similarity between myocardial toxoplasmosis and Chaga's disease.

Toxoplasmosis should be excluded in all forms of obscure myocarditis and especially in familial cardiomegaly and idiopathic hypertrophy. In the event of death every effort should be made to isolate the organism by mouse inoculation of the finely ground myocardium.

Addendum

A fifth case, a working farmer, aged thirty-four has recently presented. Cardiomegaly was found during examination before emigration. He was symptomless, apart from palpitation since the age of 15, for which he was investigated in 1940 with no clinical or cardiographic abnormality except tachycardia. Now there is general cardiomegaly and cardiograms show left ventricular stress. Toxoplasmosis dye test positive 1/16; complement fixation test positive 1/8. Thyroid activity normal. The rest of his family are being investigated.

We are most grateful to Dr. I. A. B. Cathie for the serological investigations and to Dr. A. L. Jacobs and J. D. O'D. Lavertine for details of the sister of Case 1 and for the photograph of her heart. We are also much indebted to Dr. N. R. Barrat of Cambridge for arranging for the photomicrographs to be done in his department.

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THE BALLISTOCARDIOGRAM IN THE DIAGNOSIS OF CORONARY ARTERIAL DISEASE

BY

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Deciding whether chest pain is of cardiac origin is sometimes one of the most difficult problems confronting the cardiologist. Although the electrocardiogram is generally abnormal following prolonged cardiac pain, it affords no help in over 50 per cent of cases of angina of effort (Wade and Morgan Jones, 1951), while the more rigorous methods of electrocardiographic investigation such as the two-step exercise test (Master, 1935) or the anoxæmia test (Levy *et al.*, 1940), which depend upon the production of acute myocardial ischæmia, are not entirely free from risk.

A new approach to this problem was made by Starr and Wood (1943) who applied the ballistocardiograph to the study of 55 cases of acute infarction or chronic angina pectoris. This instrument, which measures some of the forces transmitted to the body by cardiac contraction, had first been utilized by Henderson in 1905 and again by Abrahamson in 1933, but its fuller development is due to the work of Starr and his co-workers (Starr *et al.*, 1939).

Within recent years several papers have been published, mainly in America, concerning the use of the ballistocardiograph in the study of coronary arterial disease and most workers have concluded that it is a useful diagnostic aid. It has not, however, been exploited by cardiologists on this side of the Atlantic and apart from the paper of Jacobs (1954) no parallel studies have been reported in Great Britain. It is the purpose of this paper to report the results of a ballistocardiographic survey of 197 patients considered to be suffering from coronary vascular disease; to evaluate the ballistocardiograph as a diagnostic aid in this condition, and to contrast it with the electrocardiograph. Another 38 patients of corresponding age group but presumably free from cardiovascular disease have also been examined.

Material and Methods

The material consisted of 235 patients attending the University Department of Cardiology at the Royal Infirmary, Manchester, during 1952, 1953, and 1954. Thirty-eight were considered to be free from cardiovascular disease: the remaining 197 were selected because they complained of chest pain having the typical features of cardiac pain in accordance with the criteria set out by Wade and Morgan Jones (1951). Clinical myocardial infarction was considered to have occurred if cardiac pain had at some time persisted for more than one hour, for detailed histological examination of the myocardium has usually revealed infarction if cardiac pain has persisted for more than thirty minutes (Snow, 1955). Cases of valvular disease were excluded. The patients were divided clinically into three groups.

(1) Pure angina of effort.
(2) Angina of effort complicated by clinical myocardial infarction.
(3) Clinical myocardial infarction without angina of effort.

In addition to the usual clinical examination, all patients were screened and an electrocardiogram comprising standard leads, augmented unipolar limb leads, and six chest leads in the positions one to six

using the central terminal of Wilson, was taken on the same day as the ballistocardiographic study. The electrocardiograms were classified in accordance with generally accepted criteria. These criteria have been set out in full by Wade and Morgan Jones but may be briefly restated.

(1) The presence of abnormal Q waves or the absence of R waves together with changes in the S–T segment or inversion of the T wave in leads facing the left ventricle, was regarded as diagnostic of infarction.

(2) Records showing abnormal Q waves or absent R waves but without corresponding abnormalities of ST–T; or T wave inversion of a form and distribution not explicable by left ventricular enlargement, digitalis, etc. were classified as suspected infarction.

(3) Records showing S–T depression and diphasic T waves over the left præcordium, with or without delay in the onset of the intrinsic deflection, were classified as abnormal but non-specific. Conduction defects alone were also put in this group.

(4) Normal records.

It is beyond the scope of this paper to discuss in detail the merits and demerits of the various types of ballistocardiographic beds; for a good review, reference should be made to Gubner *et al.* (1953). It appears probable that the high-frequency undamped Starr bed is the most suitable for detecting qualitative changes, for in the low-frequency critically damped bed of the Nickerson type (Nickerson and Curtis, 1954) the frequency response decays too quickly leading to reduced amplitude, phase displacement, and increased duration (Rappaport *et al.*, 1953). The low-frequency, critically damped bed possesses certain advantages if it is desired to estimate the cardiac output. Our ballistocardiograms were taken on a high-frequency undamped instrument of the type described by Starr *et al.* (1939) having a natural frequency of 11 c/s. It was calibrated so that a longitudinal force of 500 g. displaced the spot 1 cm. The movements of the bed were recorded electronically together with a simultaneous electrocardiogram. The studies were made not less than two hours after a meal and patients rested for at least 20 minutes before the records were taken. The instrument was recalibrated on each occasion.

The Interpretation of the Ballistocardiograms

Ballistocardiography is still in its early and experimental stages and the approach remains empirical. If the results are to have any meaning it is therefore imperative that the criteria used in the analysis of the records should be clearly set forth.

The normal ballistocardiogram complex consists of four major and three minor waves (Fig. 1A). The nomenclature has been laid down by the Committee on Ballistocardiographic Terminology (Starr *et al.*, 1953). It is generally accepted that the major waves I, J, and K are produced by the recoil of ventricular ejection, impact in the arch of the aorta and the pulmonary artery together with recoil from acceleration down the descending aorta, and impact in the iliac and femoral arteries respectively (Starr *et al.*, 1939; Hamilton *et al.*, 1945; Starr *et al.*, 1950). The genesis of the remaining major wave H, is less certain. It is related in time to the fourth component of the first heart sound (Thompson *et al.*, 1953), and therefore to the onset of isometric contraction (Starr and Wood, 1943; Tannenbaum *et al.*, 1952; Tannenbaum *et al.*, 1954). It may well be affected by movements of blood within the ventricles at this stage of the cycle. The minor waves L, M, and N are related to diastolic events and are of less importance. There is a phasic variation in the amplitude of the complexes during the respiratory cycle due to changes in venous return, the complexes being larger in inspiration (Fig. 2A).

The ballistocardiogram may be affected quantitatively by a general slowing of the rate of cardiac ejection, a shift of the cardiac ejection curve to the "right", for it has been conclusively demonstrated that the event most closely concerned with the genesis of the ballistocardiogram is the rate at which the ventricles can accelerate their contents (Starr *et al.*, 1950). Cadaver experiments showed that the ballistocardiogram consists of the algebraic sum of two curves, one derived from ventricular discharge and the other from events happening in the aorta and to a lesser extent in the pulmonary artery (Starr *et al.*, 1950). It is therefore a measure of cardiac "force", and Starr and Schnabel (1954) have found that $\sqrt{I+J}$ corrected for surface area is closely related to the maximum velocity of ejection. Despite this correlation, force in this context appears to us to be a

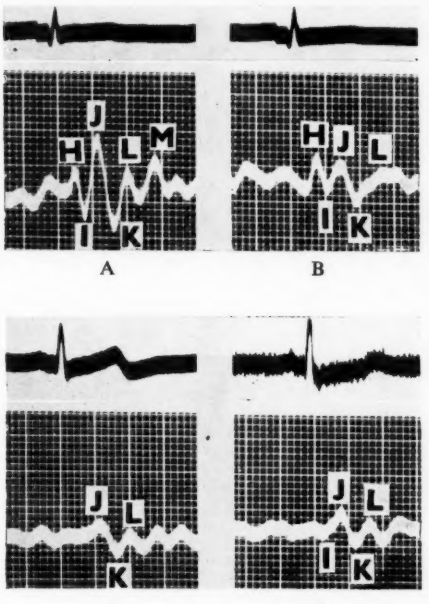


FIG. 1.—*Normal and abnormal ballistocardiogram complexes.* (A) is a normal complex; (B), (C), and (D) are abnormal complexes of the " early M," " late M," and " late downstroke " types respectively.

relative concept incorporating the resistance against which the force is acting. It is also possible that the anatomical position of the heart may affect the amplitude of I–J. Using a table capable of movement in both head/foot and lateral planes, Dock (1954) found that in hypertension a diminution in the amplitude of the major waves in the head/foot direction was accompanied by a reciprocal increase in the lateral plane; this was not so in the abnormal records of infarction. Tannenbaum *et al.* (1954) using a three-plane spatial vector-ballistocardiogram, also concluded that the amplitude of H, I, and J could be influenced by the anatomical position of the heart. For these reasons we have not used equations of the type devised by Starr *et al.* (1950) and Starr and Schnabel (1954) for the calculation of cardiac force from the ballistocardiogram.

Qualitative changes provide evidence of irregular ejection and therefore by inference of myocardial disease, and we have regarded records as abnormal only when qualitatively abnormal complexes were present. In deciding what constitutes an abnormal complex we have followed the recommendations of Starr and Wood (1943). They identified three main types of abnormal complex, the " early M " type, the " late M " type, and the " early downstroke " type. The early M complex (Fig. 1B) is due to exaggeration of H together with a small I and low J waves. In the late M complex J is split and K almost absent while in the late downstroke type J is absent and K is delayed and deep (Fig. 1C and 1D). The nature of the deformation of the ejection curve responsible for these complexes has been extensively investigated in cadaver experiments (Starr *et al.*, 1950). In the more severe disease states the complexes may become virtually unrecognizable. Abnormal complexes tend to appear first in the expiratory phase. The reasons for this are uncertain but

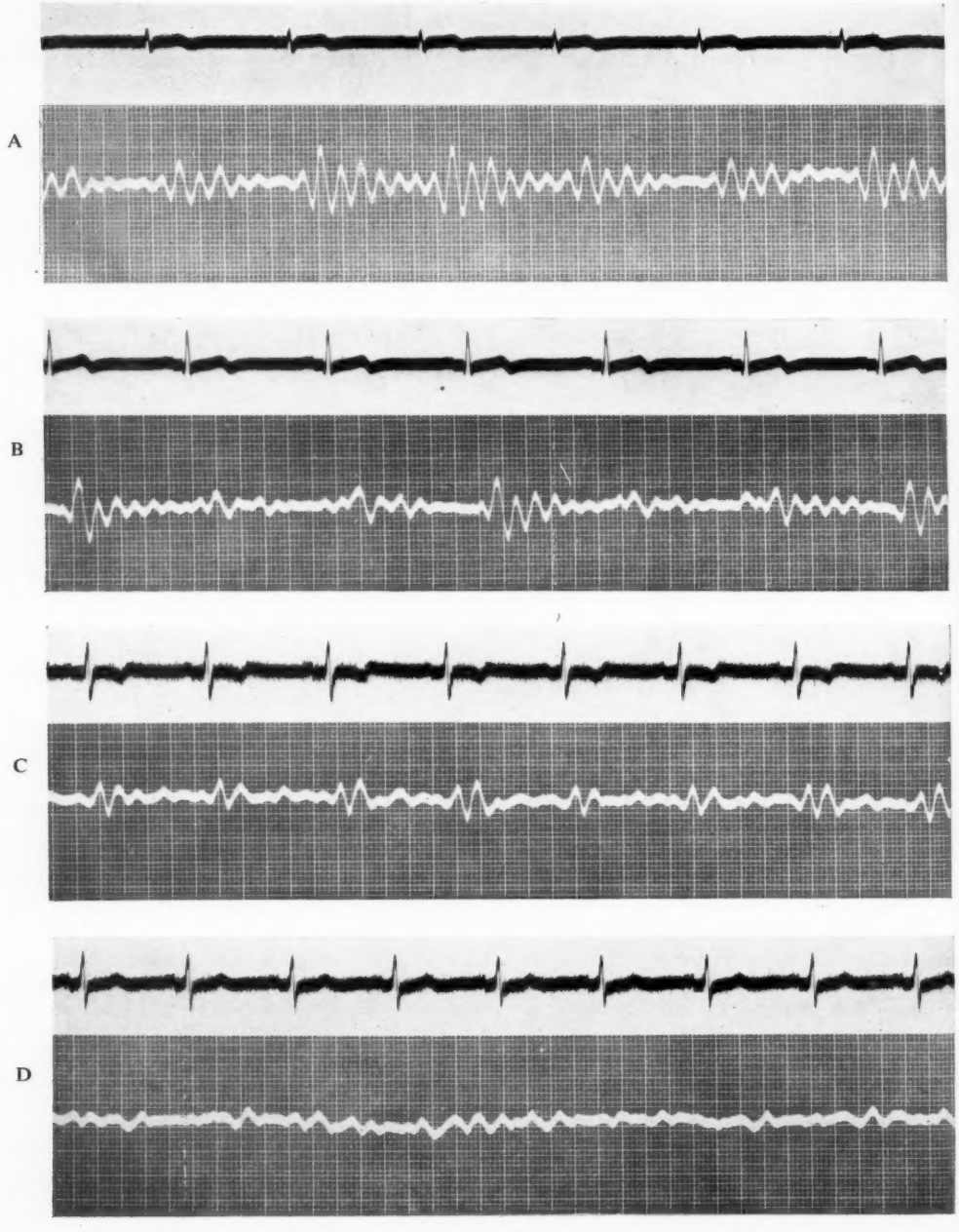


FIG. 2.—*Normal and abnormal ballistocardiograms.* (A) is a normal record showing the customary variation in complex size during respiration. The remaining records are abnormal. (B) shows early M complexes in expiration and is classified as Grade I. In (C) all the complexes are abnormal but repeatability is maintained; this is classified as Grade II. In (D) the complexes do not show a regular pattern and this is regarded as Grade III.

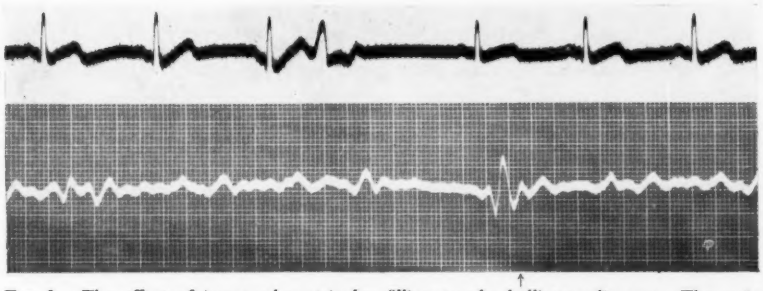


FIG. 3.—*The effect of improved ventricular filling on the ballistocardiogram.* The only normal complex, marked with an arrow, is that following a compensatory pause.

variations in venous return may be important. That improved ventricular filling may be responsible for producing a normal complex in an otherwise abnormal record is well shown in Fig. 3 in which the only normal complexes were those following the compensatory pause after an extrasystole. Any system must therefore take into account the proportion of abnormal complexes in the record.

To meet these various requirements we have therefore used the following classification. A ballistocardiogram was regarded as abnormal if any of the three types of abnormal complex described by Starr and Wood (1943) were present in the strip of recording. It was then sub-divided into grades of abnormality as follows.

Grade I. Abnormal complexes in expiration only.

Grade II. All complexes abnormal but definable and repeatable.

Grade III. Bizarre records in which repeatability is lost or in which the complexes can only be defined with the aid of the timing electrocardiogram.

Typical examples of each of these three grades are illustrated in Fig. 2 B, C, and D.

RESULTS

Cases of Coronary Arterial Disease. The results in the various clinical groups are given in Tables I, II, and III. The ballistocardiographic is more constant than the electrocardiographic pattern, the major B.C.G. difference between the three clinical groups being the higher proportion of

TABLE I

ANGINA OF EFFORT WITHOUT CLINICAL INFARCTION

No. of cases	Age group	Electrocardiogram				Ballistocardiogram			
		Normal	Non-specific	Suspected infarction	Infarct	Normal	Gd. I	Gd. II	Gd. III
23	<50	14	5	1	3	11	9	2	1
54	50–59	29	19	3	3	11	23	18	2
28	>60	16	9	1	2	1	11	13	3
105		59 (56%)	33 (31·5%)	5 (4·8%)	7 (7·7%)	23 (21·9%)	43 (41%)	33 (31·4%)	6 (5·7%)

Grade III records amongst the cases of myocardial infarction. Grade III records tend to be found more often shortly after infarction (Table IV) and it was observed that in 13 cases in which a ballistocardiogram was recorded within three months of infarction and repeated after a further three to six months, three of the four initial Grade III records had improved to Grade II or Grade I.

TABLE II

CLINICAL INFARCTION WITHOUT ANGINA OF EFFORT

No. of cases	Age group	Electrocardiogram				Ballistocardiogram			
		Normal	Non-specific	Suspected infarction	Infarct	Normal	Gd. I	Gd. II	Gd. III
20	<50	3	2	1	14	8	7	1	4
12	50–59	1	2	3	6	0	5	4	3
6	>60	1	0	0	5	0	0	4	2
38		5 (13%)	4 (10%)	4 (10%)	25 (67%)	8 (21%)	12 (31·6%)	9 (23·7%)	9 (23·7%)

TABLE III

ANGINA OF EFFORT WITH CLINICAL INFARCTION

No. of cases	Age group	Electrocardiogram				Ballistocardiogram			
		Normal	Non-specific	Suspected infarction	Infarct	Normal	Gd. I	Gd. II	Gd. III
16	<50	1	2	2	11	2	5	3	6
27	50–59	7	6	5	9	5	10	10	2
11	>60	1	2	4	4	0	4	6	1
54		9 (17%)	10 (18·4%)	11 (20·4%)	24 (44·4%)	7 (13·%)	19 (35%)	19 (35%)	9 (17%)

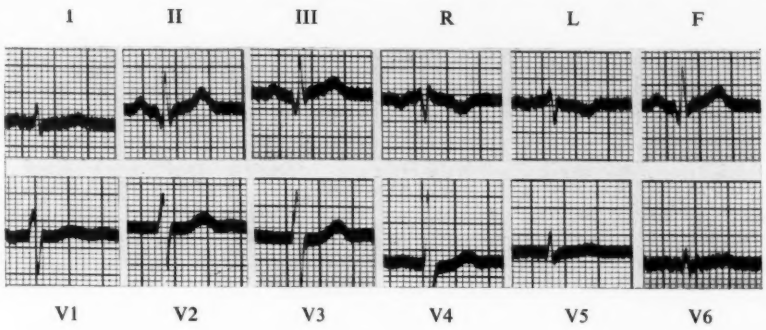
TABLE IV

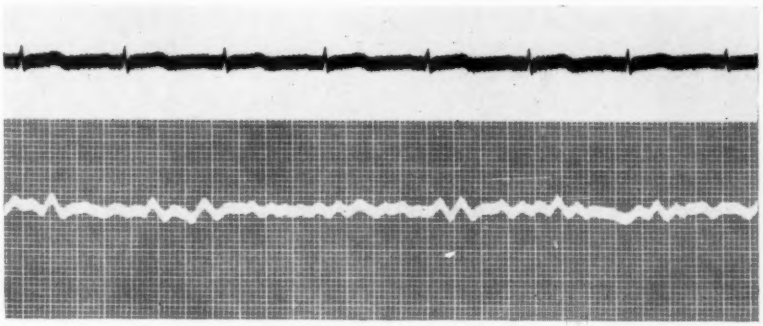
THE PROPORTION OF ABNORMAL BALLISTOCARDIOGRAMS IN RELATION TO THE TIME AFTER CLINICAL MYOCARDIAL INFARCTION

Time (months)	No. of cases	Ballistocardiogram			
		Normal	Gd. I	Gd. II	Gd. III
<3	39	6 (15·4%)	8 (20·5%)	14 (35·9%)	11 28·2%)
>3	62	14 (22·6%)	24 (38·7%)	19 (30·6%)	5 (8·1%)

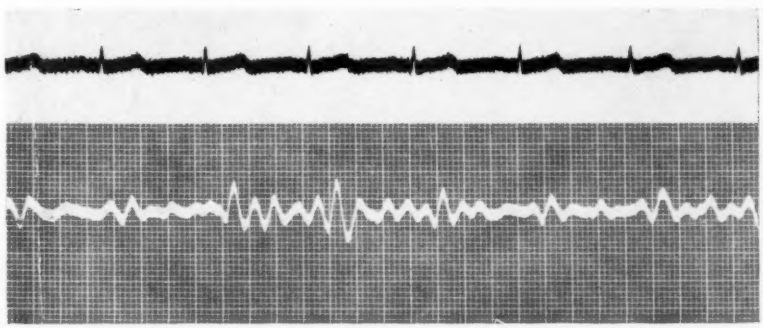
Case Report (221). A man of 48 experienced an attack of severe crushing retrosternal pain lasting several hours; his doctor reported that he was shocked. Three days later there were no abnormal findings, the electrocardiogram was within normal limits but the ballistocardiogram was Grade III. Six months later he had made a complete recovery and the ballistocardiogram had improved to Grade I (Fig. 4).

There tend to be more abnormal ballistocardiograms in the older age groups and this is well shown in the total figures (Table V). There is only one normal ballistocardiogram in the 45 patients over 60 years of age but no corresponding increased frequency of abnormalities in the electrocardiogram pattern.





Electro- and ballisto-cardiograms 3 days after infarct. (Gd. III)



Ballistocardiogram 6 months after infarct. (Gd. I)

FIG. 4.—*Grossly abnormal ballistocardiogram shortly after infarction.* The electrocardiogram and the upper ballistocardiogram were taken three days after a prolonged attack of typical cardiac pain. Apart from a doubtful Q wave in the foot lead and small voltage complexes over the left præcordium the electrocardiogram is normal but the ballistocardiogram is Grade III. Six months later the ballistocardiogram had improved to Grade I and the patient was symptom free.

TABLE V

ALL CASES OF CORONARY ARTERIAL DISEASE

No. of cases	Age group	Electrocardiogram				Ballistocardiogram			
		Normal	Non-specific	Suspected infarction	Infarct	Normal	Gd. I	Gd. II	Gd. III
59	<50	18	9	4	28	21	21	6	11
93	50–59	37	27	11	18	16	38	32	7
45	>60	18	11	5	11	1	15	23	6
197		73 (37%)	47 (10·8%)	20 (10·2%)	57 (29%)	38 (19·3%)	74 (37·6%)	61 (31%)	24 (12·1%)

That ballistocardiogram and electrocardiogram measure differing aspects of cardiac function and are not therefore interdependent is illustrated by the following cases.

Case Report (23). A man of 66 had experienced typical angina of effort for six months. A month previously he had had an attack of pain at rest lasting two hours. On examination there were no abnormal findings, the electrocardiogram showed anteroseptal ischæmia but the ballistocardiogram was within normal limits. One year later he was unchanged; an electrocardiogram was now within normal limits but the ballistocardiogram was abnormal.

Case Report (26). A man of 39 had suffered from typical angina of effort for four months. On examination there were no abnormal findings. The electrocardiogram was normal but the ballistocardiogram was Grade II. Three months later he had a clinical infarction. A year later his exercise tolerance was the same as when first seen; the electrocardiogram now showed a posterior infarct but the ballistocardiogram was still Grade II (Fig. 5).

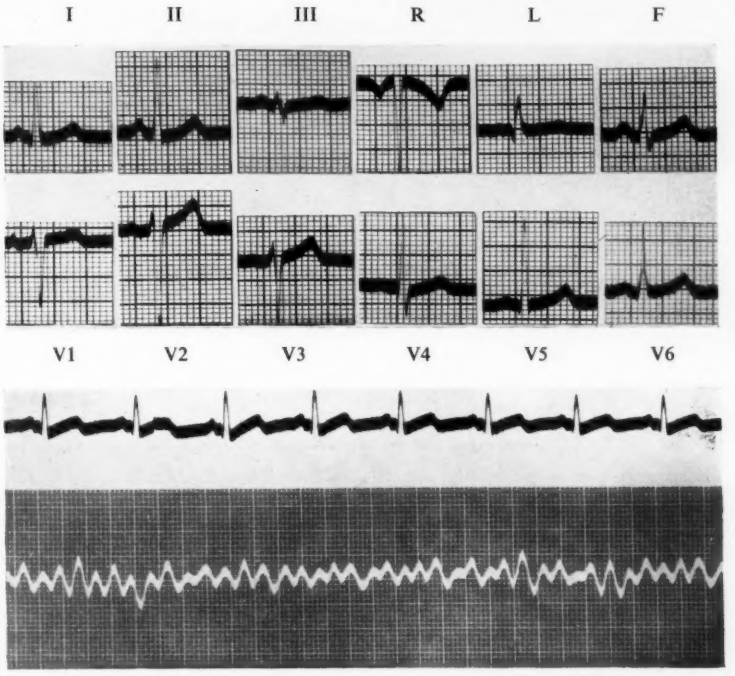
The lack of close relation between the electrocardiographic and ballistocardiographic patterns is brought out in Table VI. In this table the effects of age are discounted and the ballistocardiogram

TABLE VI

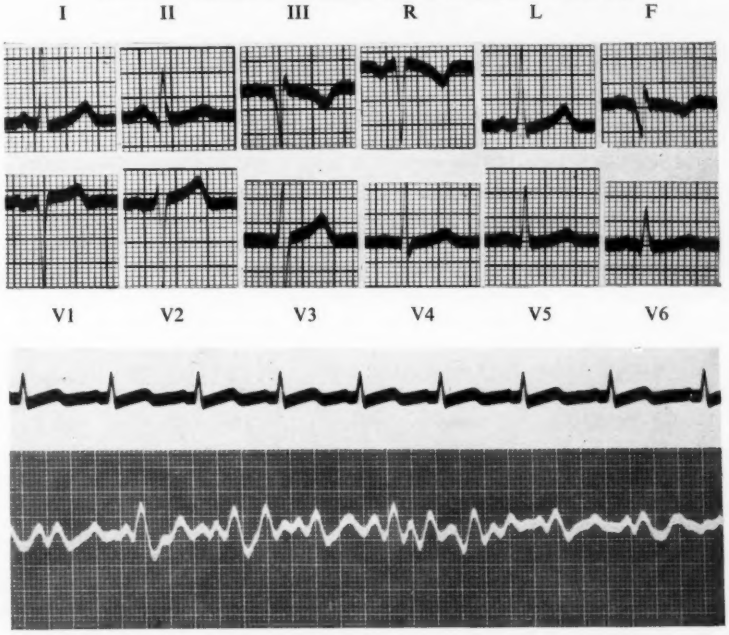
CASES OF CORONARY ARTERIAL DISEASE CLASSIFIED BY THE ELECTROCARDIOGRAM

No. of cases	Electrocardiogram	Ballistocardiogram			
		Normal	Gd. I	Gd. II	Gd. III
73	Normal	15 (20·5%)	29 (39·7%)	23 (31·6%)	6 (8·2%)
47	Non-specific	11 (23·4%)	15 (31·9%)	15 (31·9%)	6 (12·8%)
20	Suspected infarct	3 (15%)	10 (50%)	6 (30%)	1 (5%)
57	Infarction	9 (15·8%)	19 (33·3%)	16 (28·1%)	13 (22·8%)

results are very similar in the differing electrocardiographic groups. As already noted, there is a higher proportion of Grade III records in the infarction group possibly explicable in part by the time relation to the infarction. Approximately the same ballistocardiographic results were found in those cases complicated by systemic hypertension despite the very different electrocardiographic pattern (Table VII). There appeared to be a general, but not very close, relation between the grade of the ballistocardiogram and the severity of the symptoms. Thus on review in six to twelve months after the first record, over 50 per cent of the patients had not changed clinically irrespective



E.C.G. and B.C.G. 3 months before infarction (B.C.G. Gd. II).



E.C.G. and B.C.G. 6 months after infarction (B.C.G. Gd. II).

FIG. 5.—*Abnormal ballistocardiogram preceding infarction and not further affected by it.* The upper records were taken four months after the onset of angina of effort; the electrocardiogram is normal but the ballistocardiogram is Grade II. Three months later infarction occurred with diagnostic changes in the foot lead but neither the severity of the symptoms nor the ballistocardiographic appearance were altered.

TABLE VII

CASES OF CORONARY DISEASE COMPLICATED BY HYPERTENSION
(Diastolic B.P.>104 mm. Hg)

No. of cases	Electrocardiogram				Ballistocardiogram			
	Normal	Non-specific	Suspected Infarction	Infarct	Normal	Gd. I	Gd. II	Gd. III
41	11 (26·8%)	19 (46·3%)	6 (14·6%)	5 (12·3%)	5 (12·3%)	13 (31·7%)	19 (46·3%)	4 (9·7%)

TABLE VIII

THE BALLISTOCARDIOGRAM BY CONTRAST WITH THE CLINICAL STATE ON REVIEW IN SIX TO TWELVE MONTHS TIME

No. of cases	Ballistocardiogram	Clinical state		
		Unchanged	Better	Worse
40	Unchanged	26	9	5
15	Improved	11	4	0
16	Worse	9	1	6

of ballistocardiographic changes, but in only one case did the ballistocardiogram alter inversely to the clinical state (Table VIII).

Approximately one-fifth of all patients had a normal ballistocardiogram. Although most usually found in patients relatively fit, an almost normal ballistocardiogram was occasionally recorded despite severe disability.

Case Report (252). A man of 52 had suffered from severe angina of effort and high blood pressure for over five years. Six months previously he had an electrocardiographically proven myocardial infarct. He was admitted to hospital in left ventricular failure with gallop rhythm and crepitations at both lung bases. The blood pressure was 185/140 mm. Hg. The electrocardiogram showed evidence of both posterior and anterior infarction but apart from an unusually large diastolic wave and rather high voltage H waves, the ballistocardiogram was within normal limits. He made an excellent recovery from the episode of left ventricular failure and his subsequent course will be watched with interest (Fig. 6).

Fourteen patients had both normal electrocardiograms and ballistocardiograms. Five were found to be symptom-free a year later and both records were still normal in four (in one the ballistocardiogram was inadvertently omitted): Two patients had deteriorated symptomatically but both records remained normal. One patient was unchanged but the ballistocardiogram was now Grade I abnormal. The other six patients have not been seen again.

Controls. Of the 38 controls, the ballistocardiogram was normal in 37 and Grade I in one. Seventeen of these patients were under fifty and 21 between fifty and fifty-nine.

DISCUSSION

The ballistocardiogram and the electrocardiogram measure entirely different aspects of cardiac function, neither being specifically related to disease of the coronary arteries. The difference in the electrocardiographic and ballistocardiographic findings in the various clinical groups is an expression of this fact. The relation between the two methods of investigation has been dramatically described by Starr. In analogy to a motor engine he said the electrocardiogram may be

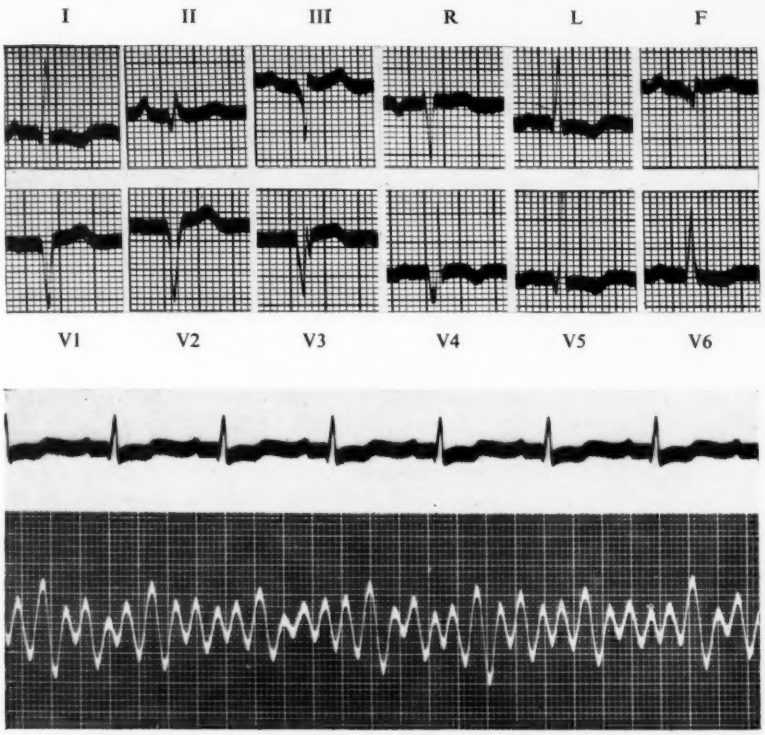


FIG. 6.—*Relatively normal ballistocardiogram despite severe myocardial disease.* There is electrocardiographic evidence of both posterior and anterior infarction and a history of left ventricular failure. The ballistocardiogram shows only minor abnormalities with large H waves in the expiratory complexes.

regarded as estimating the strength of the spark; the ballistocardiogram the resulting explosion. This concept of the ballistocardiogram as a measure of the strength of contraction offers an acceptable explanation for the fairly constant results in the various groups for it is reasonable to expect contractile power to depend as much upon the general state of the myocardium as upon the occurrence of specific infarction. The higher incidence of very abnormal records in the immediate post-infarction period suggests that infarction may initiate a long period of myocardial dysfunction and offers a further reason for gradual convalescence of patients with this condition. It might be anticipated that the ballistocardiogram would be more closely related to the severity of the disease state than the electrocardiogram and the results in the different groups tend to support this concept. It is possible, as Starr (1952) has suggested, that the ballistocardiogram may prove to have some prognostic value, but more follow-up studies are required to clarify this point.

The overall results, which show that approximately 80 per cent of patients with coronary arterial disease have an abnormal ballistocardiogram, correspond with the results reported by other workers (Chensky *et al.*, 1951; Moser *et al.*, 1952; Scarborough *et al.*, 1952; Jacob, 1954). Chesky *et al.* and Scarborough *et al.* also divided their patients according to whether there had been infarction or not and found similar ballistocardiographic results in the two groups. Brown *et al.* (1950) reported abnormal ballistocardiograms in all 27 cases of typical angina pectoris irrespective of the

electrocardiogram but the relation to infarction was not specifically stated. All these authors concluded that the ballistocardiogram was a useful diagnostic aid.

The higher proportion of abnormal ballistocardiograms in the older age groups has also been commented on by Pordy *et al.* (1951), Scarborough *et al.* (1952) and Starr and Mayock (1948). Scarborough *et al.* (1952) concluded that the increase was simply related to age and paralleled the changes found in normal subjects: they suggested that an abnormal ballistocardiogram had little or no significance in patients over 60 years of age. Starr and Mayock (1948) found an increasing proportion of abnormal records in presumptively normal men up to the age group 50–59; in that decade it reached 25 per cent, remaining constant thereafter: they felt that the group studied was in fact selected and biased in favour of heart disease. In a careful follow-up study of 80 healthy adults over ten to fifteen years, Starr and Hildreth (1952) did not observe any qualitative change in the ballistocardiogram with advancing years; there was a general diminution in the amplitude of I–J; compared with young adults there was an average decrease of 30 per cent over the age of forty, of 40 per cent over fifty, and of 49 per cent over sixty. They concluded that this was merely an expression of the fact that the ageing heart "lifts its load more slowly". We lack adequate controls over the age of sixty, but our results in normal subjects in the sixth decade suggests that Starr and Hildreth's view is correct. Scarborough *et al.* do not give their ballistocardiographic criteria so that detailed comparison is impossible, but it appears likely that they were regarding this physiological diminution in the size of the complexes with advancing age as abnormal. Jacobs (1954) has suggested that peripheral arteriosclerosis may be as important as coronary artery disease in the production of abnormal graphs. Three of our controls had what was considered to be an excessive degree of generalized atherosclerosis, but all had normal ballistocardiograms. Starr and Mayock (1948) believe that when qualitative changes are present it is probable that the coronary circulation is diseased although the subject may appear to be in good health, an opinion also put forward by Brown *et al.* (1950) with which we are inclined to concur.

In cases of systemic hypertension the diminished likelihood of finding unequivocal electrocardiographic evidence of infarction renders the ballistocardiogram particularly useful in the elucidation of the nature of chest pain. Abnormal ballistocardiograms were found just as often amongst the group with normal, non-specific or left ventricular electrocardiograms as those with definite evidence of ischæmia or infarction. The finding of a normal ballistocardiogram in 11 cases and in all four of the control group with diastolic blood pressures over 105 mm. Hg excludes the possibility that qualitative changes may be produced solely by the high peripheral resistance.

It is concluded that the ballistocardiogram is a useful diagnostic aid in cases of suspected coronary arterial disease. It is, however, dependent upon cardiac force and, in the way we have used it, is an indirect measure of the form of the cardiac ejection curve. It must be stressed that abnormalities of cardiac ejection may only be ascribed to coronary disease if other causes have been excluded. Although it appears to be a somewhat more sensitive index of coronary disease than the electrocardiogram, a normal ballistocardiogram does not exclude coronary disease. It will never supplant the electrocardiogram for it measures a different aspect of cardiac function, but even in the present early stage of its development it is a valuable complementary investigation. Of our patients with undoubted coronary disease 37 per cent had a normal electrocardiogram and 19 per cent had a normal ballistocardiogram: only 7 per cent had both a normal electrocardiogram and ballistocardiogram. It is of especial value in cases of cardiac pain confined to effort and in cases complicated by systemic hypertension. It has the additional merits of being perfectly safe, easily performed, and applicable to seriously ill patients.

Summary

The results of ballistocardiographic studies in 197 cases of clinical coronary arterial disease and 38 presumptively normal controls are reported and contrasted with the clinical and electrocardiographic data. A high-frequency undamped ballistocardiograph of the Starr type was used.

The ballistocardiogram was abnormal in 159 cases (81%). It was normal in the remainder and in 37 controls. The electrocardiogram showed changes of infarction in 77 cases (40%) and non-specific abnormalities in a further 47 (24%). It was normal in 73 cases (37%) and in all 38 controls.

The pattern of the ballistocardiographic results was fairly uniform irrespective of clinical or electrocardiographic evidence of infarction or complicating systemic hypertension. There was a tendency to a higher proportion of grossly abnormal ballistocardiograms in the immediate post-infarction phase.

Abnormal records occurred more often in the older age groups and were an expression of a higher incidence of generalized coronary disease.

The ballistocardiogram is a useful investigation in cases of suspected coronary disease, especially in cases with cardiac pain confined to effort or with systemic hypertension, for in these cases the electrocardiogram is frequently normal. Only 7 per cent of all cases had both a normal ballisto-cardiogram and electrocardiogram.

Our thanks are due to Professor Crighton Bramwell and Dr. Morgan Jones for their criticism and advice and for permission to examine patients under their care.

The ballistocardiographic table and the electronic recording apparatus were constructed by Mr. V. Attree of the Department of Electrical Engineering of the College of Technology, Manchester University.

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THE LATE INTRACARDIAC R WAVE AND THE PRÆCORDIAL PATTERN OF RIGHT VENTRICULAR HYPERTROPHY

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There is no generally accepted explanation of the mainly positive initial deflections seen in the right præcordial electrocardiogram in right ventricular hypertrophy. McGregor (1950) found in Fallot's tetralogy that whereas the initial deflections in right præcordial leads were of the rsR′ form or rsR′s, direct leads from the right ventricular epicardium were rS in type. He suggested that these mainly positive deflections from the right side of the chest arose from the left ventricle as a result of rotation, or from an area near the right atrio-ventricular groove. Carouso *et al.* (1952) obtained tall, late positive deflections (rsR′) in direct leads from the epicardium on either side of the right atrio-ventricular groove in five patients with right ventricular hypertrophy. Similar complexes from the same area in normal animals had already been reported (Groedel *et al.*, 1947).

Several workers interested in human intracardiac electrography have noted that although the ventriculogram obtained from the cavities and great vessels of the right heart is usually mainly negative, sometimes a late, mainly positive deflection is obtained. Kossman *et al.* (1950) found that in normal patients these late intracardiac R waves (qR or rsR′) were sometimes recorded from the right ventricle, sometimes from the lower part of the right atrium, or from the pulmonary artery just above the pulmonary valve. They found that deflections of this type in the pulmonary artery or right atrium were reversed on movement of the catheter into the right ventricle, and they argued that this implied that the deflections were caused by depolarization of muscle near both the pulmonary and tricuspid orifices, for example, the *crista supraventricularis*. They suggested that hypertrophy of this muscle might be responsible for the late positive deflections obtained from right præcordial leads in right ventricular hypertrophy.

In patients with right ventricular hypertrophy Kroop *et al.* (1951) found this rsR′ (or rsR′s) pattern just above the pulmonary valve, and in the right atrium; they did not obtain it from the right ventricle. It was not recorded from the pulmonary artery in normal hearts. They, too, pointed out its similarity to the pattern found in leads V1 and aVR in right ventricular hypertrophy, and suggested that it might be caused by depolarization of the right ventricular surface. Sodi-Pallares *et al.* (1951), discussing the late R sometimes recorded from within the right atrium, suggested that it arose from the late activation of muscle high in the septum, and they stated that in right ventricular hypertrophy these right atrial patterns were like those recorded from the right præcordium.

This paper records the incidence of the late intracardiac R wave in 50 patients, and correlates its occurrence and amplitude with right ventricular pressure and form of ventricular complex in the conventional electrocardiographic leads V1 and VR.

Material and Methods

During the cardiac catheterization of 50 cases of congenital and acquired heart disease simultaneous records were made of electrocardiographic leads VR and V1, the intracardiac electrogram,

and intracavity pressure. The technique, using an electrode-tipped catheter was as previously described (Emslie-Smith, 1955). The diagnoses are shown in Table I. None of the patients had cardiac failure at the time of catheterization; the patient with constrictive pericarditis had a normal right ventricular pressure pulse.

TABLE I

INCIDENCE OF LATE INTRACARDIAC R IN 50 CASES

Diagnosis	Number of cases	Number of cases with late intracardiac R
Mitral stenosis	22	16
Constrictive pericarditis	1	0
Pulmonary stenosis (including Fallot's tetralogy)	18	10
Patent ductus arteriosus	2 (1 with reversed shunt)	0
Ebstein's anomaly	1	1
Complex congenital cardiac lesion not fully diagnosed	6	6
TOTAL	50	33

The tracings were recorded as a rule during slow withdrawal of the catheter tip from the pulmonary artery to the right atrium. In analysis of the curves, the shape of the ventricular complex in leads V1 and VR, and the site, form, and amplitude (mV) of any late intracardiac R were noted, and the right ventricular systolic pressure (mm. Hg) was measured with reference to the end-diastolic pressure.

RESULTS

The results are summarized in Tables II and III which contain all the data from which the correlations discussed below were calculated. The frequency of occurrence of late intracardiac R in various sites is shown in Table IV.

Correlation of Late Intracardiac R with Right Ventricular Systolic Pressure and with Other Features of the Electrocardiogram

The presence or absence of a late intracardiac R (Fig. 1–3) bore no relation to the height of the right ventricular pressure. In 30 cases with such an R, the right ventricular systolic pressure varied from 16 to 154 mm. Hg (mean 69) while in 17 cases with no such R wave the pressures varied from 18 to 136 mm. Hg (mean 52) (Fig. 4). Again in 19 cases in which the height of the late intracardiac R wave and the right ventricular pressure could both be measured, there was no clearly significant relationship between the two (Fig. 5). The correlation coefficient here was 0·59, the highest of many correlations encountered during this investigation, and still barely significant.

Analysis of the patterns of initial deflections in leads V1 and VR in cases with and without a late intracardiac R have shown no difference in distribution of types in the two groups. The value of the ratio R/S in lead V1 showed no statistically significant relation to the right ventricular systolic pressure in either group, nor to the amplitude of the late intracardiac R in cases with such a deflection. The form of VR bore no relationship to the height of the late intracardiac R.

Of the 10 cases with right ventricular systolic pressure over 75 mm. Hg (range 76–154 mm. Hg, mean 101) the form of the intracardiac ventriculogram showing the tallest late R resembled V1 in only one case, and was similar to VR in four cases.

TABLE II

DATA FROM CASES WITH LATE INTRACARDIAC R WAVE

RV systolic pressure (mm. Hg)	Late intracardiac R						V1		VR
	Maximum height (mV)	Form ventriculogram with maximum late intracardiac R	Site				Form ventricular complex	S/R	Form
			PA	RV	RA	Elsewhere			
16	1·4	qRs			+	SVC	rS	3·8	Q
20	2·5	QrsR′s′			+		rsRSR*		rSrsR
26		RSR′	+		+		rS	2·2	Qr
32		rsR′	+	+	+		Rs	0·2	qR
36	1·2	rsR′S′	+	+			RS*	1·0	rsRS
	0·9	qR			+		Rs*	0·7	Qr
36	4·2	rsR′		+			rS	4·2	Qr
40		rsR′s′		+					Qr
40	2·1	rsR′s′	+	+	+		Qr		Qr
42		rsR′s′		+			rS	4·6	Qr
45	1·4	qRs			+		rS	3·9	rS
48		R			+		RS	1·0	Qr
50	1·8	qRs		+					Qr
50		Qr	+	+	+		rsR	0	QR
51		rSR′	+				rS		Qr
53	1·4	QR, qR			+	Hepatic vein	R	0	qR
54	1·8	rsR′S′		+			Rs	0·3	Qr
60		qR			+		R	0	qR
60	2·5	rSR′	+		+		rS	1·3	Qr
73		R		+	+				Qr
76		rSR′S′	+	+			R*	0	QR
80	3·3	rsR′	+	+			rsR*	0	Qr
80	3·5	RsR′		+			Rs	0·5	Q
84		rsR′s′	+	+	+		RS	1·0	QR
88	2·5	rSR′	+	+			Rs	0·1	rSR
92	4·1	qR	+	+	+		rsR*		qR
100		Qr				L.A. and pulmonary vein	R*	0	
110	1·5	rsR′S′	+	+	+		Rs	0·2	QR
136	1·7	qR			+		R	0	
144	4·9	R	+	+			Rs	0·1	Q
154	4·2	qR			+		R	0	qR
	2·1	Rs			+	Hepatic vein	R	0	qR
		QR			+†		rSRs*		QRsr

* Indicates complete right bundle-branch block.
† Only the RA was explored.

Eight of the 50 patients had complete right bundle-branch block: all showed a late intracardiac R. It was found that the pattern RSR′ or a variant occurred in the initial deflections of the intracardiac lead showing a tall late R in about half the cases irrespective of the presence or absence of right bundle-branch block. It would therefore appear that an intracardiac lead of the form rsR′ is not indicative of bundle-branch block.

No secondary R waves (R′) were apparent in V1 in any patient whose intracardiac electrogram showed no late R. Conversely in 29 cases without right bundle-branch block and showing a late intracardiac R only one showed a secondary R in lead V1.

DISCUSSION

It has been suggested that in right ventricular hypertrophy the patterns obtained from the right præcordial, or right unipolar arm, leads are related to intracardiac late positive deflections (Kossman *et al.*, 1950; Kroop *et al.*, 1951; Sodi-Pallares *et al.*, 1951). This study offers no support for

TABLE III

DATA FROM CASES WITHOUT LATE INTRACARDIAC WAVE

RV systolic pressure (mm. Hg)	V1		VR
	Form ventricular complex	S/R	Form
18			Qr
24	rS	1·9	Q
26	rS	1·9	rS
30	R	0	Qr
30	R	0	qR
32	Rs	0·7	QR
32	RS	1·0	Qr
36	rS	2·2	Qr
45	Q	—	Q
50	rS	3·0	Qr
52			
56	rS	6·5	Q
56	R	0	qR
62	rS	2·6	Q
85	R	0	Qr
119	R	0	
136	R	0	Qr

TABLE IV

INCIDENCE OF LATE R IN VARIOUS INTRACARDIAC SITES

Site	RV alone	RA alone	PA alone	PA+RV	RA+RV	RA+PA	RA+PA+RV
Number of cases	6	11	1	5	1	2	6

Late intracardiac R recorded from RA in 20 cases
,, ,, ,, ,, ,, RV ,, 18 ,,
,, ,, ,, ,, ,, PA ,, 14 ,,

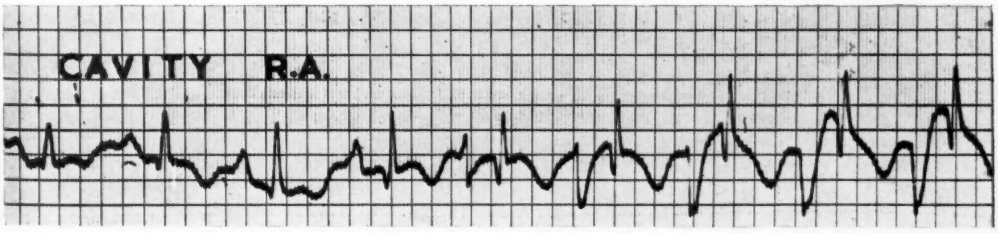

FIG. 1.—Right atrium (low, middle, and high positions). Intracardiac electrogram shows late R in ventriculogram at all levels.

this hypothesis. A high incidence (66%) of late intracardiac R was found in this series of patients, most of whom had lesions commonly associated with right ventricular hypertrophy. (Its incidence in subjects with normal hearts, or in patients with left ventricular hypertrophy is not known.) No significant relationship was found between the occurrence or height of the late intracardiac R and either the right ventricular systolic pressure or the form of the ventricular complex in leads V1 or VR.

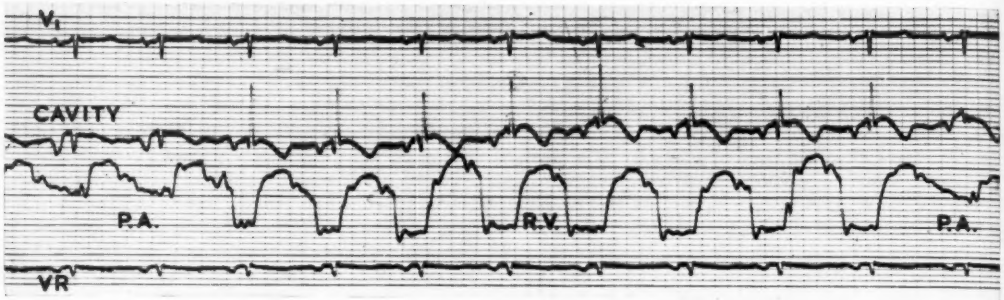

FIG. 2.—Catheter tip moving from PA to RV and back in a case of mitral stenosis. Above downwards: ECG lead V1, intracardiac electrogram, pressure, ECG lead VR. High, late intracardiac R in RV.

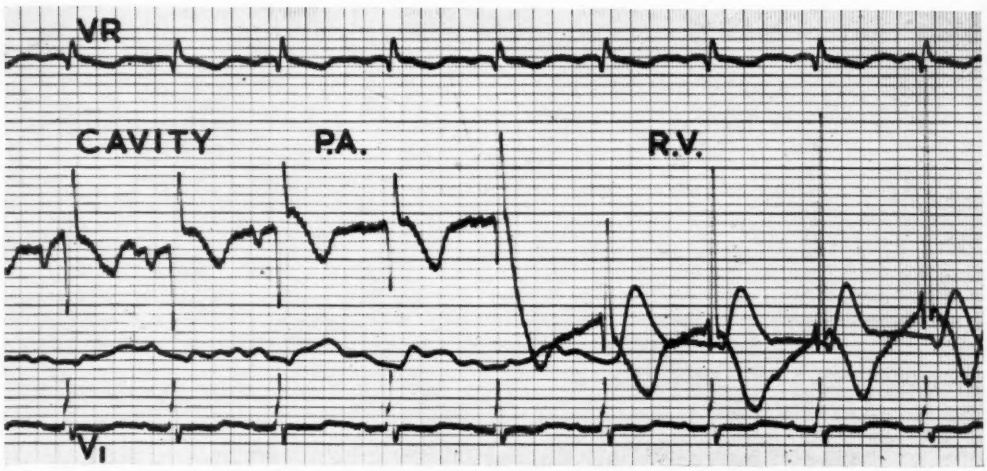

FIG. 3.—Catheter tip moving from PA to RV in a case of pulmonary stenosis. Above downwards: ECG lead VR, intracardiac electrogram, pressure, ECG lead V1. Late intracardiac R in PA and (high voltage) in RV. (The inverted T of the ventriculogram crosses the upright right ventricular pressure pulse.)

Kossmann *et al.* (1950) considered that the vector arising from depolarization of the *crista supraventricularis* in normal hearts produced both the late intracardiac R and certain deflections sometimes recorded by surface leads: for example, secondary r from the right præcordium. They suggested that hypertrophy of the *crista* might cause the high, late præcordial R of right ventricular hypertrophy. It might also be expected to cause a high, late intracardiac R. For this reason the amplitude of the late intracardiac R was measured in this investigation. From the inverse square law it is apparent that the amplitude of a deflection recorded by an exploring electrode is very dependent upon the distance between the electrode and the source of the e.m.f. in the contracting tissue. High amplitude intracardiac deflections may therefore indicate simply that the electrode is very near a portion of contracting muscle; consideration of the method employed here shows that it is not possible to determine within a few millimetres the position of the electrode within the ventricular cavity in its relation to, for example, the *crista supraventricularis*.

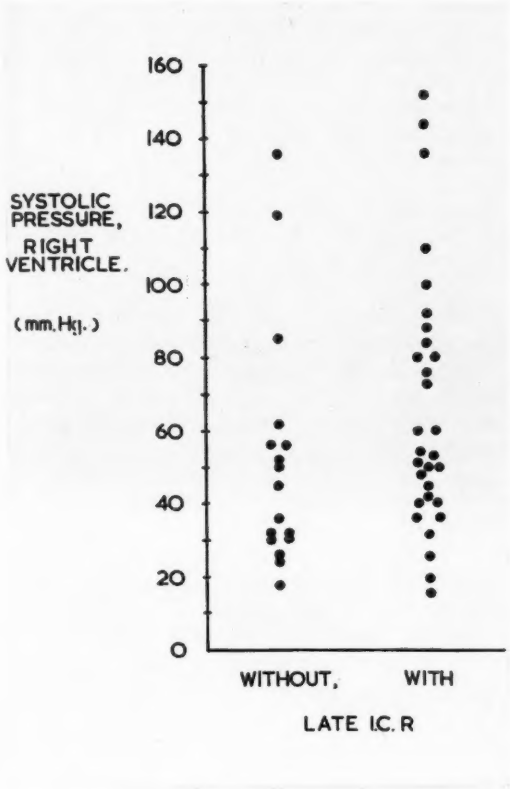

FIG. 4.—Right ventricular pressures in cases with, and without, a late intracardiac R.

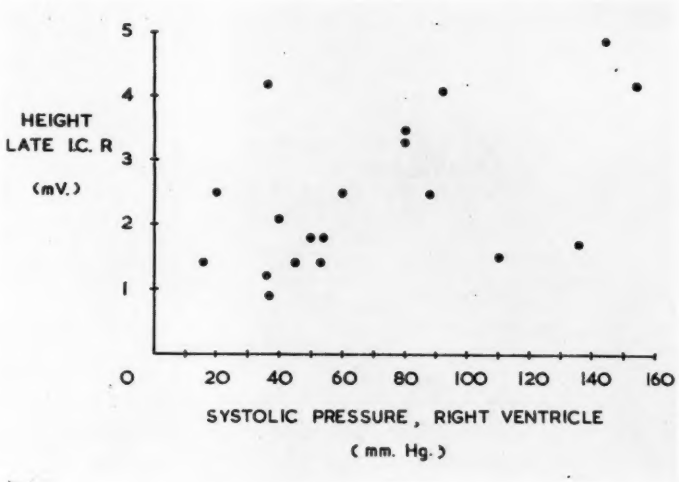

FIG. 5.—Right ventricular pressure and height of late intracardiac R (correlation coefficient = 0·59).

Camerini and Davies (1955) have recently suggested that the secondary R (r) which they consider to be a normal finding in some right præcordial leads may be related to the late intracardiac R. In this investigation a secondary R in V1 was not seen in the group that did not show a late intracardiac R, but was present in five cases of the group that did show a late intracardiac R. Four of these cases showed complete right bundle-branch block, and in three of them the intracardiac ventriculogram with the tallest late R did not show a secondary R. However, only V1 was examined, and a præcordial secondary R might have been commoner in either group had other right præcordial leads been examined.

In cases of right bundle-branch block a late intracardiac R may be expected from septal depolarization above and below the block (Sodi-Pallares *et al.*, 1948). The removal of the eight cases of right bundle-branch block from this series does not alter the significance of any of the correlations.

Summary

The intracardiac electrogram has been recorded from 50 patients during cardiac catheterization. A late intracardiac R was recorded in 33 cases, most commonly from right atrium and right ventricle. No significant relationship appears to exist between the occurrence or amplitude of this R and either the right ventricular systolic pressure or the form of the ventricular complex in leads V1 or VR.

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ANEURYSM OF THE AORTIC SINUSES WITH PSEUDO-COARCTATION OF THE AORTA

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Aortic sinus aneurysms are uncommon; association with pseudocoarctation has not been previously recognized. Morgan Jones and Langley (1949) in a classic paper reviewed forty-three autopsy proven cases, added four new ones, and divided them into congenital and acquired types: of the total, twenty-five were congenital. Venning (1951) reported three additional cases and Falholt and Thomsen (1953) in describing a case of unruptured congenital right aortic sinus aneurysm diagnosed by retrograde aortography increased the number of congenital sinus of Valsalva aneurysms to thirty-four. Recently, Besabe *et al.* (1954) reported a case of congenital aortic sinus aneurysm with rupture into the right atrium and embolic gangrene of a foot; at necropsy ulcerated bacterial endocarditis of a bicuspid aortic valve was found.

Sixteen cases of unruptured aortic sinus aneurysms have been diagnosed during life by angiocardiography at this centre. Seven were congenital, three associated with coarctation of the aorta (Dubilier *et al.*, 1955), one other with coarctation of the aorta and subacute bacterial endocarditis (Steinberg and Finby, 1955), three with arachnodactyly (Steinberg and Geller, 1955), and nine acquired, due to syphilis (Merten *et al.*, 1955). The seventeenth case of unperforated aortic sinus aneurysm herein reported is unique because of the association with pseudo-coarctation of the aorta.

Case Report

A 26-year-old married sewing-machine operator referred by Dr. Raymond Miller was admitted with complaint of backache of two years duration. When 13 years old, she had aching bones and joints unaccompanied by fever for a week. The next year she fainted on two occasions and after examination was told she had "rheumatism of the heart." Her activities were restricted and she was well until two years ago when she was in a motor accident. Although the car in which she was a passenger overturned, she sustained only superficial injuries to the thorax; and since then has had much backache. There had been no dyspnœa, orthopnœa, or œdema, and in addition to her household duties she had been steadily employed.

Physical examination showed a well developed and nourished woman in no distress. The only abnormal finding was a grade III systolic murmur heard all over the base of the heart, loudest along the left sternal border and transmitted to the neck and axilla. A loud systolic murmur was also heard along the course of the aorta posteriorly and at the epigastrium. The radial, abdominal, femoral, popliteal, and dorsalis pedis pulses were palpable. Blood pressure readings were: right arm, 126/90; left arm, 130/90; right leg, 140/120; and left leg, 132/110.

Laboratory data were as follows: hæmoglobin, 12 g. per 100 ml.; erythrocytes, 4·6 m. /cu. mm.; hæmatocrit, 38 per cent; the differential blood count and smear were normal. The electrocardiogram showed normal sinus rhythm, rate 88 a minute, no deviation of the electrical axis, P–R II=0·16 sec. and QRS II= 0·07 sec. The standard limb and unipolar leads were normal and the heart was in the vertical position.

The frontal teleroentgenogram (Fig. 1A) showed slight left ventricular prominence. A mass (arrow) was seen above what appeared to be a dilated aortic knob. Rib notching was not detected. The left anterior oblique view revealed bowing of the posterior wall of the trachea by a dilated descending aorta

* Aided by a grant from the Mallinckrodt Chemical Works.

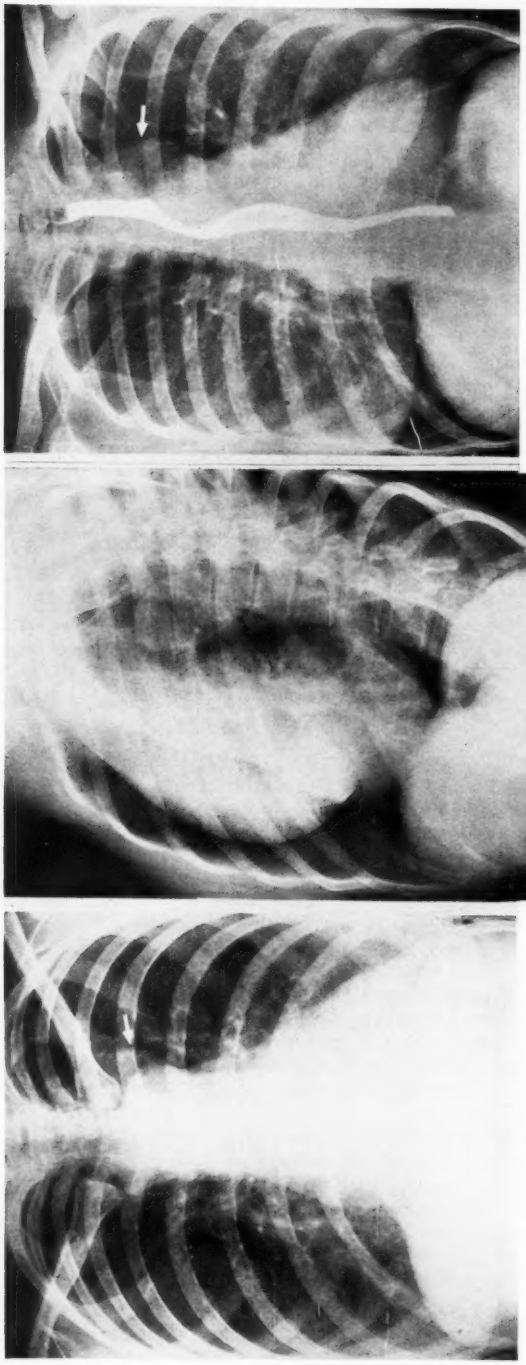
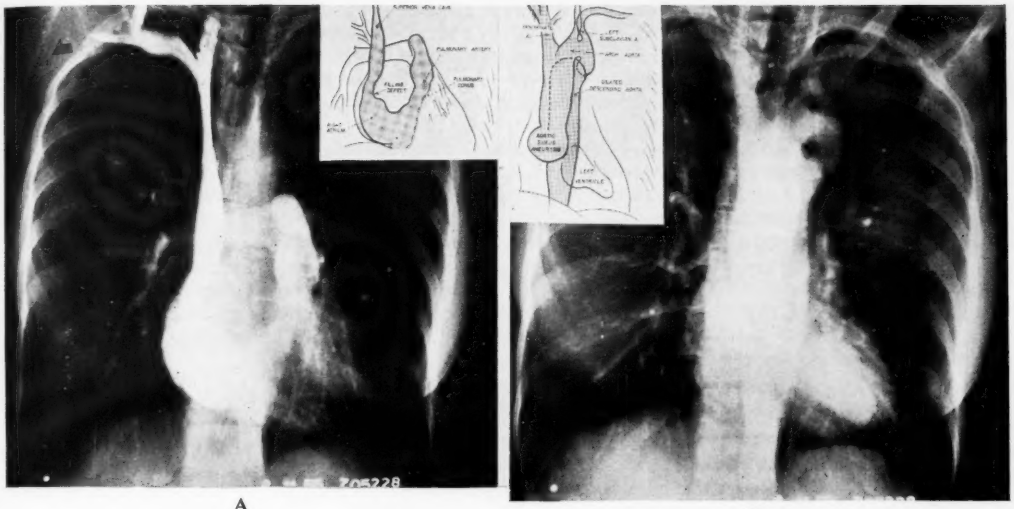
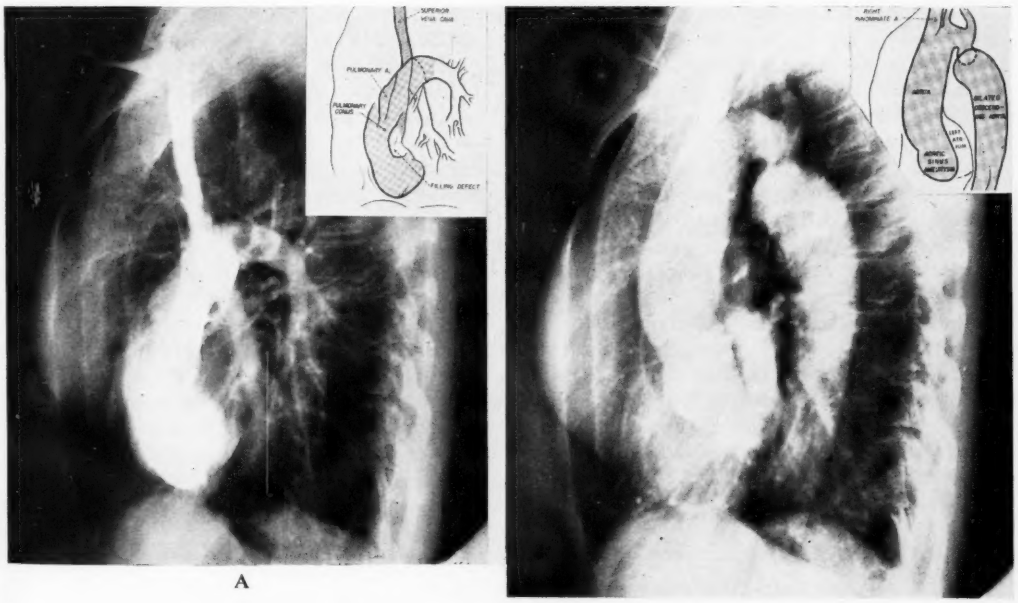


FIG. 1.—(A) Conventional frontal teleroentgenogram shows some prominence of the left ventricle. A mass (arrow) is present above what appears to be an aortic knuckle. (B) Left anterior oblique view shows anterior bowing of the posterior wall of the trachea by a dilated descending aorta. (C) Frontal œsophagram shows indentation of the œsophagus by a dilated descending aorta; a mass just above is indicated by arrow. No rib notchings are seen.



A B

FIG. 2.—(A) Frontal angiocardiogram at 1·5 seconds after the beginning of injection shows opacification of normal right cardiovascular structures. Note the indentation of the superior vena cava. (B) At 7 seconds, the left cardiovascular structures are opacified. Note the aneurysmal dilatation of the aortic sinuses, the dilated ascending aorta and aortic arch and left brachiocephalic vessel anomalies. The descending aorta is dilated but arterial collaterals are not present.



A B

FIG. 3.—(A) Left anterior oblique angiocardiogram at 1·5 seconds. The right cardiovascular structures are normal. Note the filling defect adjacent to the superior vena cava and outflow tract of the right ventricle. (B) At 7 seconds, the aneurysmal dilatation of the aortic sinuses, the dilated ascending aorta and deformed aortic arch and dilated descending aorta are demonstrated. The internal mammary arteries are of normal size.

(Fig. 1B); while the frontal œsophagram showed deviation of the œsophagus by the same structure (Fig. 1C). On radioscopy the left supra-aortic mass appeared to be expansile and pulsatile.

Serial angiocardiography disclosed slight displacement of the terminal end of the superior vena cava at its entrance into the right atrium (Fig. 2A). A deformity of the superior part of the right atrium was also seen in Fig. 3. Fig. 2B and 3B showed that the filling defect adjacent to the superior vena cava was due to the aneurysmal dilatation of the aortic sinuses which measured 50 mm. in diameter. The ascending aorta (Fig. 2B and 3B) appears dilated and measured 40 mm. (average normal 38 mm.). The innominate artery was also dilated (20 mm.) and the transverse aorta abruptly narrowed and became rounded with a dilated (10 mm.) left subclavian branch at its upper pole. Below, the descending aorta became large and bulbous measuring 45 mm. in diameter. The dilated contour continued almost to the diaphragm. The internal mammary arteries were visualized and appeared normal in calibre. No collaterals were recognized (Fig. 3B)

Simultaneous direct brachial and femoral arterial pressure recordings were made and interpreted by Dr. Daniel S. Lukas. The readings were: brachial artery, 117/86 (mean 105); femoral artery, 119/86 (mean 102). A suggestive anacrotic limb and moderate rounding of the systolic phase of the brachial arterial pressure curve was present; but was not distinctive enough to warrant the diagnosis of aortic stenosis. The onset of systole in the femoral artery was 0·04 sec.

Discussion

The aortic sinuses are three small dilatations in the wall of the aorta immediately above the valves. Each sinus lies just above the attachment of an aortic cusp. The right and left coronary arteries usually originate within two of the aortic sinuses; however, they may emerge immediately distal to the aortic sinuses. The aortic sinuses and their corresponding aortic valves are named according to the source of the coronary arteries. Thus, the right and left coronary arteries arise from the right and left aortic sinus respectively. The remaining aortic sinus usually lies posteriorly and does not contain a coronary artery and according to the newest nomenclature is designated the non-coronary sinus.

The aortic sinuses are intracardiac and cannot be identified on conventional roentgenography. During angiocardiography they appear as dilatations at the root of the aorta immediately above the aortic valves and are best visualized in the left anterior oblique view (Dotter and Steinberg, 1951). Inconstant filling of the coronary arteries during angiocardiography does not always allow individual identification of the sinuses. However, in the left anterior oblique view the right coronary sinus is regularly anterior and just behind the sternum. The aortic sinuses are in close relation to all the cardiac chambers, particularly the right atrium and ventricle. The origin of the pulmonary artery, the interventricular septum, and left atrium are adjacent while the superior vena cava is more distant.

Anomalies of the aortic arch and descending aorta may simulate a superior mediastinal tumour. Sanders *et al.* (1951) reported three such cases: their first was found to have a short patent ductus arteriosus which was ligated but failed to affect the aortic deformity; the two others were suspected after conventional roentgenography and confirmed in one instance by angiocardiography.

Subclinical or pseudo forms of aortic coarctation became recognizable with the advent of angiocardiography (Dotter and Steinberg, 1951). A total of ten such cases have been encountered at this centre. Usually the patient is asymptomatic and is referred because of the finding of a pulsatile mediastinal swelling. On angiocardiography the nature of the aortic deformity is clearly delineated and easily differentiated from coarctation by the demonstration of an aortic lumen and the absence of arterial collaterals. In the case herein reported (Fig. 3B) although arterial collateral vessels were absent, the abrupt termination of the aortic arch, and the dilatation of the descending aorta favoured the diagnosis of coarctation. Indeed, the diagnosis of pseudo-coarctation depended upon the absence of any change in the blood pressure in the legs.

Summary

A patient with aortic sinus aneurysm was found to have an associated pseudo-coarctation of the aorta. This is the eighth case of congenital aortic sinus aneurysm diagnosed during life by angiocardiography and the first associated with pseudo-coarctation.

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CONGENITAL HEART BLOCK

BY

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Accurate prognosis of any condition demands a knowledge of its natural history, and often this is less complete than we would wish. This is true of several congenital abnormalities of the heart and the present paper is a contribution to the natural history of congenital heart block.

In 1934 Campbell and Suzman reported 8 patients with congenital complete heart block: two of these, both with other cardiac abnormalities, died. The subsequent progress of the other six and of a seventh patient was reported by Campbell in 1943, when their ages were between 22 and 43 years.

It seems worth reporting the condition of these seven patients (referred to as Group I) after another ten years, and we have succeeded in seeing all of them except one about whom we have had replies from her and from her doctor. Their progress during these ten years will be described first, and then the cardiac findings at their recent examination. Finally, eight other patients with congenital malformations of the heart as well as heart block will be described (Group II): they have all been seen in the last few years.

The Present Condition of the Seven Patients (Group I)

One of these seven patients (Case 9) has died with an obscure cardiovascular condition since this paper was first written. The other six are still leading normal lives, with the usual variety of activity. Only one of the three women is married and she has no children. None of them has any significant cardiac symptoms so it is clear that patients can get on well for forty years or more with congenital heart block. Except for one (Case 4) who has had Stokes-Adams attacks—the last, eight years ago—they have had no illnesses that can be directly attributed to their heart block. They have, however, had at least their share of other diseases; one case of tuberculosis with a good recovery (Case 2) and one case of essential hypertension (Case 5) are perhaps no more than might be expected by chance, but two endocrine disorders, diabetes mellitus (Case 3) and myxœdema (Case 9), are perhaps more than would be expected.

In 1934 and in 1943 the heart block was complete in all these patients and so far as was known always had been. In 1955 this was still so (Fig. 1) in all except Case 7 who at some unknown date had changed from complete heart block to sinus rhythm with latent heart block (see Fig. 4). The heart was of normal size (Fig. 2) in all except Case 8 and perhaps Case 9. Case 8 was the only one who was thought to have any other cardiac abnormality and none had any evidence of a ventricular septal defect. Some details are given in Table I and for convenience of reference they have been given the same numbers as in the earlier papers.

[*Cases 1 and 6.* These two are not included in the seven followed-up as they died when five years old, one before and one soon after the paper of Campbell and Suzman (1934): both had other abnormalities of the heart.]

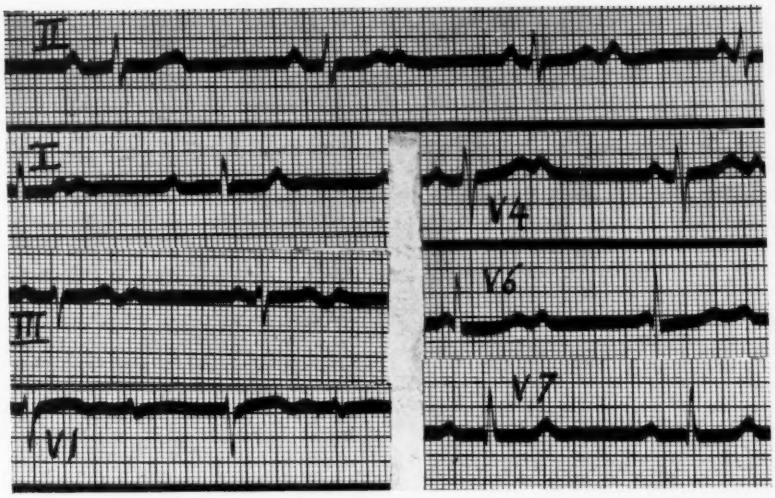

FIG. 1.—A typical electrocardiogram showing no abnormality except the complete heart block. Above, a longer run of lead II to show the heart block is complete. Case 2.

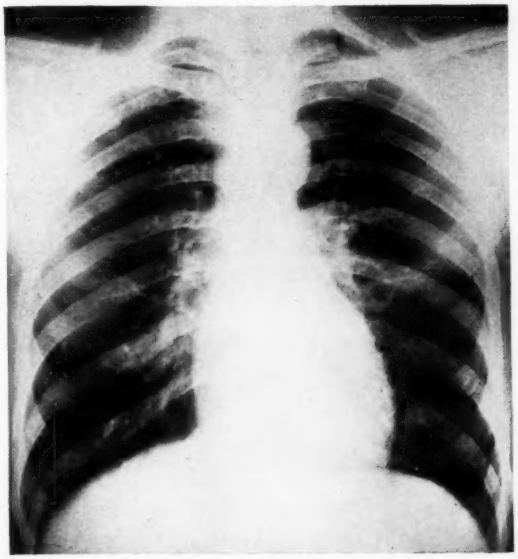

FIG. 2.—A typical small normal heart (c.t.r. 44%: m.t.d. 12·2/28 cm.) with rather prominent lung markings but no increased pulsation. This was the picture seen in most of the patients. Case 4.

Case 2. This woman, now aged 40, looks well and is of good physique. In 1938 she had pulmonary tuberculosis but soon recovered, and the radiograms of the lungs now show some small calcified areas only. She is married and leads a normal life but does not feel able to do as much as she would like, being a little breathless with the heavier housework.

Case 3. This man, now aged 35, served in the R.A.F. during the war, when he was passed for flying duties. He is now working as an electrician. In 1949 he was found to have diabetes mellitus, but with dieting and insulin he keeps fit and leads a normal life.

Case 4. This man, now aged 37 years, has kept extremely well. Although he has cut down his previous activities which were unusually energetic both at work and at play, he leads a normal and full life as a planning engineer. He is the only patient of the series who has experienced Stokes-Adams attacks but the last occurred eight years ago.

Case 5. This woman, now aged 56, did her housework and worked on a farm for twenty years, walking two miles to her work. She writes that she is still well and complains only of some tightness and wheeziness in the chest, and that she can not now work or dig or cycle as energetically as she used to. She has had no occasion to visit a doctor since we saw her last in 1927. We have been unable to persuade her to come to London but she has at our request seen her doctor. He informs us that she is overweight and has to stop sometimes on stairs or hills because of tightness in the chest and dyspnœa and she has some orthopnœa at night. Her heart is large but this is probably due to essential hypertension as her blood pressure which was 190/90 in 1927 is now 260/120 mm. Her heart rate was generally between 44 and 50 and is now 54 a minute, so it has not become slower as she has grown older.

Case 7. This woman, now aged 43, worked as a hairdresser when she was young and as an instrument maker during the war. She has given up her employment but says that she is working harder at home and is without symptoms. She is tall and stooping but looks well. To our surprise the heart rate was not the usual slow one, but was 120 a minute. An electrocardiogram showed that instead of complete heart block (Fig. 3) there was a sinus tachycardia with latent heart block,

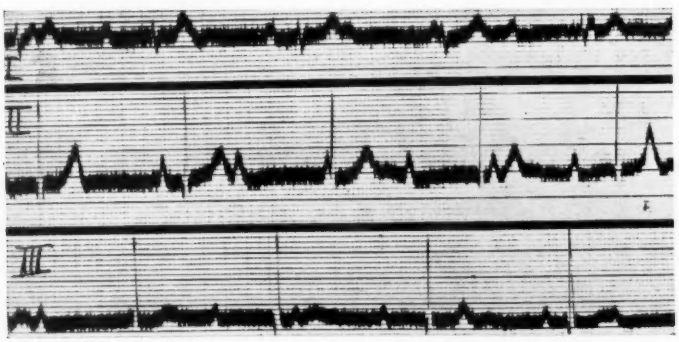

FIG. 3.—Congenital complete heart block. In 1932 the block was complete (A 86, V 46) but in 1954 it was latent (see Fig. 4). Case 7 in 1932.

the P–R interval being prolonged up to 0·44 sec. (Fig. 4). She was unaware of any difference and could not say when the tachycardia had started or what was now her usual rate, but at three subsequent visits during the next year she was still in sinus rhythm with a long P–R interval, at somewhat slower rates of between 70 and 90 (Fig. 4) and said that when at home it was now generally between 60 and 70 a minute.

Case 8. This man, now aged 38, worked exceptionally hard during the war laying concrete floors, and when younger played football for his club team and won several boxing contests. In 1949, in view of his large heart and the presence of left bundle-branch block (Fig. 5), he was advised

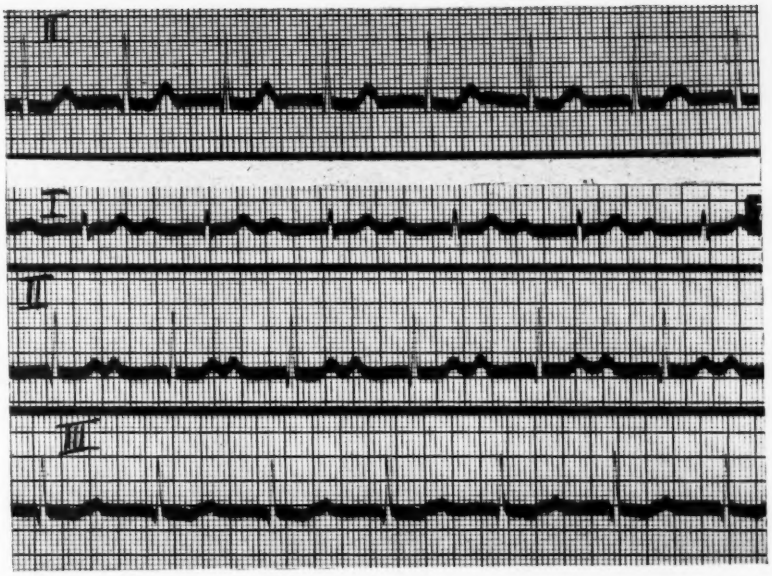

FIG. 4.—Electrocardiogram from the same patient as in Fig. 3 twenty-two years later, showing latent heart block with sinus tachycardia: the P–R interval was about 0·44 sec. Sometimes, as in the upper record, the P wave is hidden in the preceding T wave. Case 7.

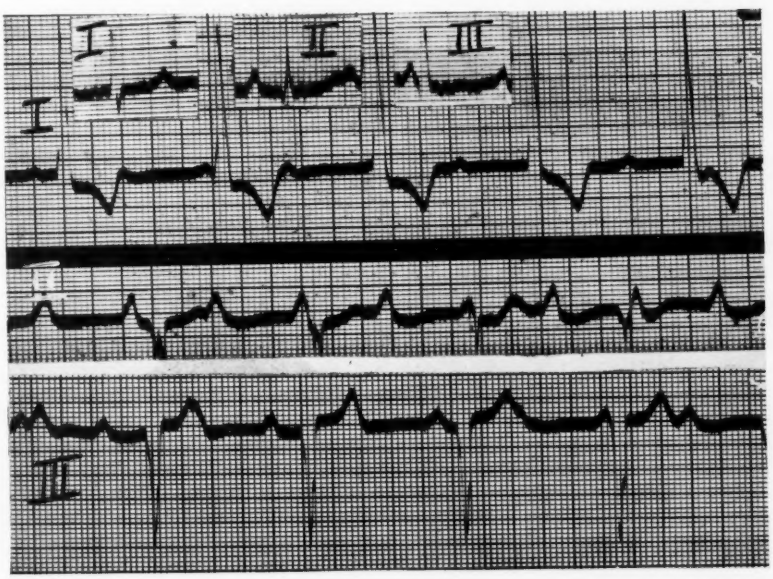

FIG. 5.—Inset above. Complete heart block with normal QRS complexes in 1933. Main figure. Electrocardiogram from the same patient fifteen years later (1948), showing left bundle-branch block, which has persisted. Complete heart block has been found throughout. Case 8.

to do less; he became a tobacconist, and though he still works a twelve-hour day he has felt better. He is somewhat breathless on strenuous exertion such as running for a bus, but he is overweight and has become bronchitic during the last five years, so that it is difficult to be certain that his symptoms are cardiac. His heart is the largest of any in this series (Fig. 6: c.t.r. 56%) but has not increased during the last six years.

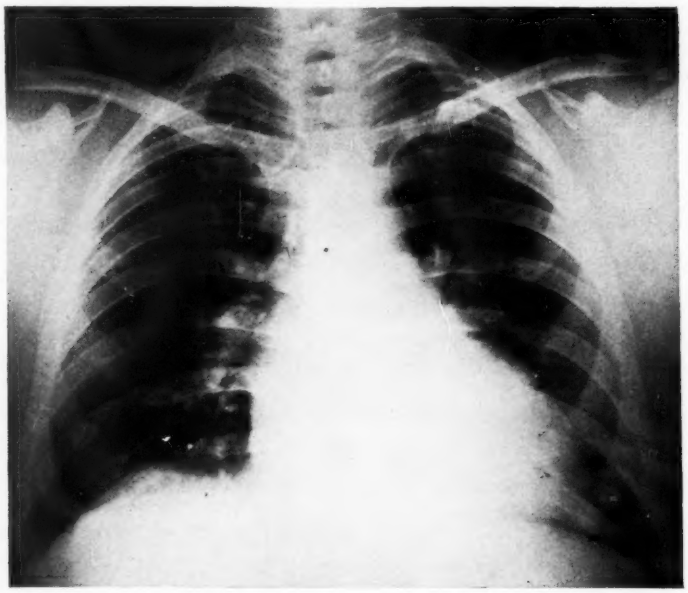

FIG. 6.—The only large heart in the series (c.t.r. 56%: m.t.d. 16·2/29 cm.). This patient had left bundle-branch block and probably aortic incompetence, which had not been present when he was younger. Case 8.

Case 9. This man, aged 49 when he died, was 29 when the diagnosis was first proved, so the heart block is less certainly congenital. When he was a child, however, his parents were told that his heart was not normal and when he was a student at Guy's Hospital he remembered having jaundice and being demonstrated as a case of bradycardia. When last reported, he was 36 years old and was leading a busy life as a dental surgeon. In 1947 he had a kidney removed for pyelonephritis.

When seen again in 1951 he had a dry skin and had been losing hair for two years; he had the appearance of myxœdema and a basal metabolic rate of −38 per cent. His heart rate (32–36) was at the lower end of his usual range, 32–42 a minute. With two grains of thyroid daily he lost all signs of myxœdema.

Earlier the same year he had some weakness of the left side and, later in the day, a speech defect from which he did not recover completely for three weeks. Since 1945, there had been two other shorter attacks, both affecting his speech and his left side: he was left-handed. He was seen by Sir Charles Symonds also who thought he had thrombosis of the right internal carotid artery but a cerebral arteriogram failed to prove this. There was no special reason to suspect recurrent emboli. No change of heart rate was noted at the time of the attacks but a slower rate or cardiac standstill might have led to cerebral ischæmia and the symptoms might have taken this form rather than the usual Stokes-Adams attacks because of some local cerebral vascular abnormality. He made a good recovery and resumed much of his work but still had difficulty with a complex word or problem.

Since this was written he has died. In November, 1954, he had pyrexia up to 100° F. and pain in the chest for a few days without hæmoptysis, but three weeks later he seemed as well as usual and no physical signs could be found. In March, 1955, the pain and pyrexia recurred, this time with hæmoptysis, and these continued. He was seen by Dr. Bodley Scott who has kindly informed us that there was no rise of venous pressure nor other signs of congestive failure, though he was somewhat orthopnœic. The heart was thought to be larger and the pulmonary second sound louder than they had been before, but the slow rate of 40, the blood pressure, and the systolic murmur were unchanged. At the right base there was impairment of percussion, crepitations, and pleural friction. No peripheral venous thrombosis could be found and it was thought that the pulmonary infarction was more probably due to primary thrombosis, helped, perhaps, by the slow heart rate. He died two days later and throughout his final illness there was no episode to suggest any Stokes-Adams attacks or any change in his heart block. Unfortunately there was no necropsy and it is difficult to be certain what part his heart block may have played in his long and complex series of illnesses.

The Findings in these Patients

Physical Signs. The murmurs and other physical signs are described in the next section, when discussing the absence of any evidence for diagnosing a ventricular septal defect.

The Size of the Heart. This was normal in all the patients (Fig. 2) except Cases 5 and 8 (Fig. 6) and perhaps Case 9. Comparing all the X-ray films did not reveal any common feature, though most of the hearts were rather small, probably because of the patients' build, and the markings in the lung fields were rather prominent: they were, however, within normal limits and there was no expansile pulsation to support the presence of a left-to-right shunt.

TABLE I

Some Details of the Seven Patients with Congenital Heart Block

Case No.	Sex	Age when slow pulse was first noticed	Age when first seen with electrocardiogram	Age at present	Heart size (cardiothoracic ratio)		Heart rate at rest				Blood pressure	
					Percentage		1933		1954			
					1933	1954	Atrial	Ventricular	Atrial	Ventricular	1933	1954
2	F	1	12	40	56	50	112	46–64	83	48–70	160/80	150/70
3	M	2	12	35	52	46	64	43–52	50–60	39–42	120/65	105/65
4	M	2	12	37	+	45	136	42–50	100	42	120/50	140/80
5	F	2	27	56	+	++	108	44–50	—	54	190/90	260/120
7	F	5	20	43	50	46	96	46–56	*	*	150/90	135/85
8	M	13	13	38	51	56	82	44–56	86	46–56	130/70	160/90
9	M	10	29	49	53	54	86	36–42	88	32–42	125/80	150/85

* Sinus rhythm 60–108 with latent heart block.
\+ Slightly if at all enlarged. ++ Enlarged.

The cardiothoracic ratios were generally about 45–50 per cent (see Table I). Twenty years before they were though to be a little larger, about 52 per cent, but we can not be sure of the accuracy of the earlier figures which were taken from orthodiagrams while the later ones are from teleradiograms. It is, however, possible that the hearts were larger when the patients were younger and were leading more active lives that called for a larger stroke volume.

The Heart Rate. The heart beats much faster than is usual in acquired heart block, 40–50 instead of 28–40 a minute (Campbell, 1944). In 1934 we thought that as the patients got older the rates might become slower and nearer to those in acquired heart block, but there is no evidence of this

so far. In 1934 the rates were generally between 42 and 52 with an average of 48 a minute: in 1954 they were generally between 40 and 50 with an average of 47 a minute. In Cases 3 and 4 there was not much increase of rate with gentle exercise, but this point was not examined as fully as in 1933.

Brown (1950) says that the rate is generally between 36 and 92: Metianu and de Balsac (1954) put it between 40 and 80 and never less than 30 a minute. They add that the atrial rate is usually over 100 which is another point of difference from acquired heart block: it was often over 100 in our cases but was often slower, especially as the patients grew older.

The Blood Pressure. The blood pressure was generally within the usual range but the pulse pressure was wider to compensate for the slow heart rate. The average pulse pressure was 67 in 1933 and 75 in 1954, or 62 and 61 respectively if the patient with hypertension is excluded. In 1927–33 the three older patients, then 27, 21, and 19 years old, had pressures of 190/90, 150/90, and 160/80: the first, now aged 56, has a pressure of 260/120 and as the diastolic has risen this probably indicates essential hypertension, but the other two have not maintained the high pressures as they have grown older and the readings are now 135/85 and 150/70.

The Electrocardiogram. This was normal apart from the heart block (Fig. 1), except in Case 8 with left bundle-branch block (Fig. 5) and Cases 3 and 4 with some tendency to left ventricular preponderance (S in V1 being 12 and 13 mm. and R in V6 being 14 and 9 mm. respectively); in Case 9 there was rather low voltage in the standard but not in the unipolar leads.

The Association with Ventricular Septal Defects

In 1934 we thought that the systolic murmur heard in most of these patients indicated a ventricular septal defect, as it was a common view that these two congenital lesions often occurred together. This point has been re-examined more critically now that the nature of the congenital heart lesions can be diagnosed more accurately. All but one of the patients had a systolic murmur but generally it seemed to be functional or cardio-respiratory rather than organic. In 1932 only one was thought to have a systolic thrill and in 1954 a thrill could not be felt in any of them. In most of them the lung markings were dense rather than light but all were within normal limits, so there was no evidence of any left-to-right shunt.

In Case 2, a systolic murmur of moderate intensity was heard in the third and fourth left interspaces but no thrill was felt, and on radioscopy the pulsation and density of the lung fields were within the upper limits of normal and there was no enlargement of either ventricle, so it is unlikely that there was any shunt through a septal defect. In Case 3 the systolic murmur was recorded as rather harsh when he was a boy, but twenty years later no murmur could be heard and the heart was small normal. In Case 4 a soft systolic murmur was heard best inside the apex but it was sharply localized and changed with respiration; no thrill was felt and the heart was of normal size and shape, so the murmur can hardly be organic.

In Case 5 there was in 1927 a systolic murmur heard best towards the apex but no thrill: in 1955 her doctor did not think the murmur significant; the heart was larger but this was probably due to essential hypertension. In Case 7 the systolic murmur was soft and could be dismissed as functional, as there was no thrill, no enlargement of the heart, and no abnormal pulsation on radioscopy. In Case 8 there was an additional lesion: there was no thrill but a moderate systolic murmur in the third and fourth left spaces from the midline to near the apex, a diastolic murmur that was easily heard above this, and a normal second sound. Probably he had aortic regurgitation though the murmur was heard rather low and on the left, the pulse pressure was no wider than in other cases, and on radioscopy both ventricles seemed enlarged. A large ventricular septal defect was excluded by the normal appearance of the lung fields on radioscopy. In Case 9 the systolic murmur was loudest and most constant near the apex though it varied with deep respiration, no thrill was felt, the heart was slightly enlarged but had not changed during eight years, and the lung fields were normal, so even a small ventricular septal defect is unlikely.

There is, therefore, no patient in whom a ventricular septal defect or any other congenital lesion

can be diagnosed with confidence. Case 8 has aortic incompetence possibly from atherosclerosis of bicuspid aortic valves and Cases 2 and 9 might have small ventricular septal defects of the maladie de Roger type but this is unlikely in the absence of a thrill. Case 3 has no murmur at all and the other three have systolic murmurs that are probably functional.

The Incidence of Congenital Heart Block

Although these patients were all seen within a few years and led us to believe that congenital heart block was more common than was generally thought, subsequent experience has not supported this view and we have seen few cases since. Among the many infants at Guy's and the Evelina Hospitals in the last thirty years we can remember only one with heart block being referred to the Cardiac Department. The heart block was sometimes 3 : 1 and sometimes 2 : 1 and he was thought to have congenital fibrocystic disease of the pancreas (Trounce and Potter, 1952).

Among the many patients with congenital heart disease that we have seen since 1947, complete or partial heart block has not been common, but has been found in 8 out of about 1800 cases. Even latent heart block is not very common, though it has been noted in several severe cases of simple pulmonary stenosis and of atrial septal defect and in some others.

Before discussing these we are reporting two other possible examples of the type seen in Group I, but the evidence is much less complete than in our earlier cases.

Case 10. A woman, aged 32 years, complained of occasional palpitation, of giddiness on change of posture, and some three years previously of some fainting attacks. There was no history of rheumatic fever or of diphtheria. Her heart rate was found to be 50–60 and on exercise rose to 90, but there was complete heart block, with an atrial rate of 100 a minute. The heart was not enlarged and there was no thrill, but a systolic murmur was heard at the apex. She was seen at intervals for two years during which time there was no change, but then she emigrated to Australia.

Case 11. A man, aged 31, who was leading an active life and playing football, was seen because of his slow heart rate. He had complete heart block with a ventricular rate of 40, but no other abnormality could be found. When in hospital eighteen years before with scarlet fever, his pulse rate had been charted between 70 and 100 a minute. Six years later he was much the same except that his blood pressure had risen from 150/85 to 180/100. He still showed complete heart block with a ventricular rate of 41 and an atrial rate of 122. The main reason against accepting his block as congenital is that he was passed for military service without comment, but Case 3 served in the R.A.F. and was passed for flying duties.

Patients with Heart Block and other Congenital Heart Abnormalities (Group II)

The other congenital abnormalities associated with heart block in these eight cases were not of any one type and there was not the usual predominence of uncomplicated Fallot's tetralogy among the cyanotic cases. Three had Fallot's tetralogy, but one with situs inversus and one in its acyanotic form. One had Eisenmenger's complex, one was thought to have tricuspid atresia, and one transposition of the aorta and pulmonary trunk. The remaining two were acyanotic: one was a classical example of atrial septal defect and the other was thought at first to have this but the diagnosis was uncertain.

In Group I the heart block was nearly always complete, but in this group who had other congenital defects it was more variable. In 5 of the 8 it was so far as we know always complete. In the sixth it was sometimes 2 : 1 and sometimes complete (Case 14), and in the seventh it was sometimes 2 : 1 and sometimes latent with a P–R interval of 0·28 sec., and later complete (Case 15). In the last we have no evidence that it was ever complete, and there was partial block with Wenkebach's periods (Case 18). We do not know that the heart block dated from birth in these cases and three of them were 30, 35, and 42 years of age when first seen, so acquired block can not be excluded but seems unlikely.

The rate when the block was complete was, in general, faster than in our patients of Group I and much faster than in acquired block, about 52 to 70 a minute, but it was only 33 in Case 12, a woman aged 42. This relatively rapid rate made it all the more difficult to say how long the block had been

present and generally it had not been recognized before we saw them. Some details about these eight patients are given in Table II and short case notes follow.

Case 12. A woman, aged 42, had been cyanosed from infancy. She had been fairly well till she was twenty and then became progressively more disabled, and when she was seen she had congestive failure. There was complete heart block with a ventricular rate of 33 a minute, and she was thought to have tricuspid atresia, but no investigations were carried out. She died two years later and there was no necropsy.

Case 13. A girl, aged 14, was thought to have Fallot's tetralogy with dextrocardia and complete situs inversus. As far as is known, her block was always complete with the ventricular rate between 50 and 60. She has got on well for four years.

Case 14. A boy, aged 12, had doubtful cyanosis and had become rather more breathless in the last year. Catheterization showed a moderate pulmonary stenosis as well as a left-to-right shunt through a ventricular septal defect: the arterial oxygen saturation was 95 per cent, so that he belongs to the group of acyanotic Fallot's tetralogy. He had complete heart block at a rate of 50–64 a minute. Later, in hospital the block was sometimes complete and sometimes 2 : 1 and his pulse rate was generally between 48 and 70 a minute.

Case 15. A woman, aged 35, had always been disabled but not seriously before she was 28, when she became worse till she could walk only a quarter of a mile. She was thought to have Fallot's tetralogy. She showed 2 : 1 heart block, but we do not know when this had developed. A year later there was latent heart block with a P–R interval of 0·28 sec. Six years later she has developed congestive failure and when she was seen there was complete heart block with a ventricular rate of 48; this was about the usual rate but it had been about 64 for three weeks some months previously.

Case 16. A woman, aged 30, was always breathless and began to notice cyanosis when she was nine; it had increased since though it was not severe. She had been finding her work as a dressmaker more difficult the last two years. The signs suggested Eisenmenger's complex with pulmonary regurgitation, and catheterization confirmed the high right ventricular pressure, though the pulmonary artery was not entered. There was complete A-V dissociation with the atrial rate 70–84 and the ventricular rate 64–73 a minute (Fig. 7).

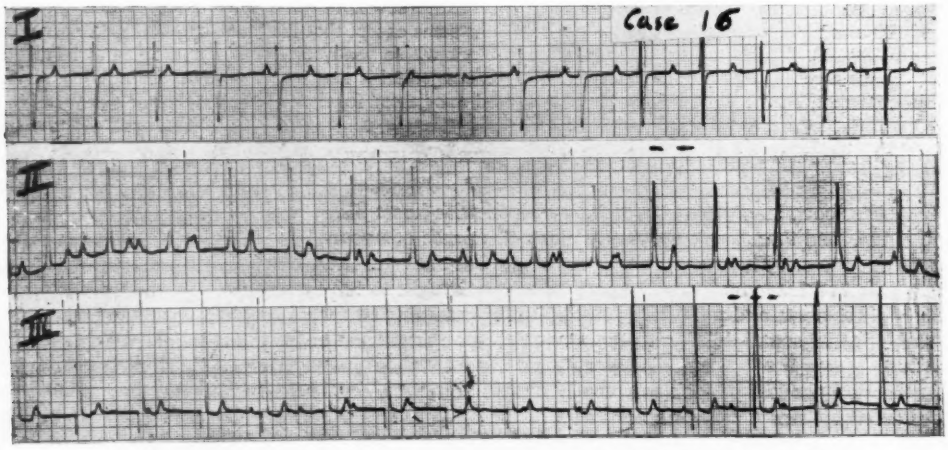

FIG. 7.—Complete heart block with a rapid ventricular rate of 64 a minute (atrial, 70). From a patient with Eisenmenger's complex. Case 16.

Case 17. A boy, aged 12, had always been cyanosed and moderately disabled though he could walk a mile slowly. The blood flow to his lungs was increased, and he was thought to have partial transposition of the aorta and pulmonary trunk. His pulse rate had always been slow and this was due to complete heart block with a ventricular rate of 60 a minute.

Case 18. A boy, aged 14, was thought to have an atrial septal defect. He had few symptoms and no comment had been made on his heart rate, but when he attended hospital the rhythm was irregular because

of partial heart block with Wenkebach's periods and dropped beats, the P–R interval lengthening from 0·26 to 0·33 sec. The condition was the same a year later (Fig. 8).

Case 19. A girl, aged 6, was not much disabled but was found to have lungs that looked pleonæmic and a large heart (c.t.r. 66% in 1950, 58% in 1955). During five years observation her heart rate was slow, due to complete heart block with the ventricular rate about 45 to 60 a minute. She was thought to have an atrial septal defect, but catheterization did not reveal any abnormality. We have, however, left her in this group because the pulmonary changes were too striking and the heart too large to accept it as normal apart from the heart block.

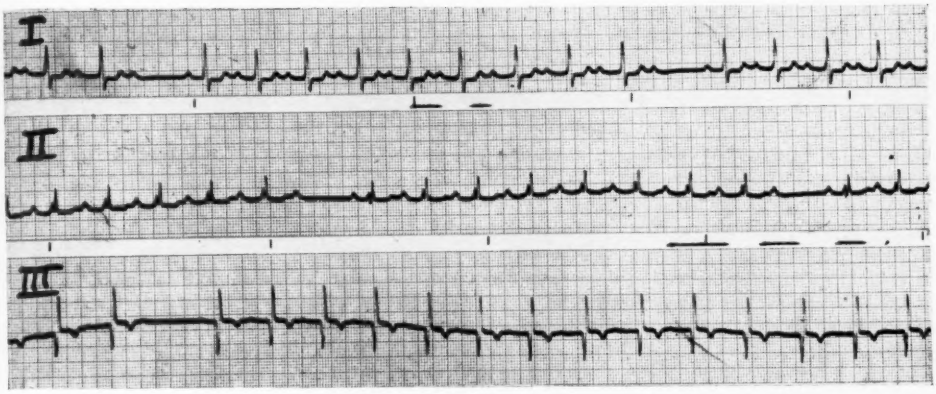

FIG. 8.—Partial heart block with Wenkebach's periods and dropped beats from a patient who showed this at both visits at a year's interval. He had an atrial septal defect. Case 18.

TABLE II

SOME DETAILS OF EIGHT PATIENTS WITH CONGENITAL HEART DISEASE AND HEART BLOCK

Case No.	Age and sex	Diagnosis	Heart size (cardio-thoracic ratio %)	Degree of heart block
12 (CB15)	F42	Uncertain, perhaps tricuspid atresia	55	Generally C.H.B. (A, 96: V, 33)
13 (CB19)	F14	Fallot's tetralogy with situs inversus	47	C.H.B. (A, 78–100; V, 50–60)
14 (O825)	M12	Acyanotic Fallot's tetralogy	52	C.H.B. (A, 110; V, 48–70) and 2 : 1
15 (O127)	F35	Fallot's tetralogy	61 *	2·1 block (P–R, 0·24 sec.) and latent block (P–R, 0·28 sec.), and later C.H.B. (A, 137; V, 47)
16 (P173)	F30	Eisenmenger's complex	57	C.H.B. (A, 70–84; V, 64–73)
17 (I312)	M12	Transposition of aorta and pulmonary trunk	56	C.H.B. (A, 85; V, 60)
18 (I035)	M14	Atrial septal defect	62	Partial H.B. with Wenkebach's periods
19 (P339)	F6	?Atrial septal defect	66–58	C.H.B. (A, 75–90; V, 45–60)

* The kyphoscoliosis was so severe that this was very uncertain.

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Discussion

The association of congenital heart block with a ventricular septal defect will be discussed first, and then the variability in degree and form of the block, and the prognosis of patients suffering from this condition.

The Presence of a Ventricular Septal Defect or other Abnormalities. It was assumed at one time that an underlying structural defect, usually a patency in the ventricular septum, interrupted normal conduction; White (1951) for example wrote "Congenital interventricular septal defects are the rule in the very rare cases of congenital heart block" and Friedberg (1950) thought it was almost always associated with such a defect. Taussig (1947) thought that it rarely occurred without some other congenital lesion but that this was a defect of the atrial septum as often as of the ventricular septum. The evidence supporting these views does not seem strong enough to merit such emphasis. Yater *et al.* (1933) for example found that signs suggestive of a ventricular septal defect were present in only 27 of the 44 reported cases of congenital heart block, and Brown (1950) found this in 51 of 77 cases but in only 5 of 12 cases with necropsy: in view of the changed views about the clinical diagnosis of ventricular septal defect the earlier figures are not reliable.

Certainly a number of cases have, at necropsy, shown a ventricular septal defect (Yater *et al.*, 1934; Towers and Bremer, 1947; and Clark and White, 1952). Among the eleven necropsies quoted by Wallgren and Winblad (1951) the following abnormalities were observed; a defect of the ventricular septum in six cases, amounting to cor triloculare in three, with or without other associated defects, partial transposition of the heart and viscera in one, and patency of the inter-atrial septum in three. One of these last three and one other who had no associated abnormality had a fibrous interruption of the bundle of His. These, however, have been a selected group in whom a relatively early death was probably associated with an unusually high incidence of serious structural defects. Of our eight patients with congenital heart disease and with heart block (Group II), each of the six cyanotic patients had a ventricular septal defect among the other abnormalities but the two acyanotic patients had not.

The presence of a ventricular septal defect is no reason for expecting to find heart block and this is true even when there is a single ventricle and no ventricular septum (Campbell *et al.*, 1953). Monckeberg (1924) showed that in nearly all cases of ventricular septal defect, even when the septum is completely absent, the bundle is conserved though its position may be abnormal. Furthermore there have been many reported cases of heart block where the diagnosis of ventricular septal defect has not been made and others where it may be questioned. The finding of a thrill is unusual, and even when a præcordial systolic murmur has been recorded it is by no means certain that it indicates the presence of such a defect. Fisch (1948) for example has suggested that it might be due to an increased stroke volume secondary to the bradycardia; while Sprague and White (1927) did not think that the systolic murmur in four of their series of patients with complete block justified the diagnosis of the block as congenital and described it simply as idiopathic. Leach (1930) thought there was no good evidence that the lesion was usually a defect in the ventricular septum.

Finally, it has been suggested that the block is due not so much to a hole in the septum as to the presence of fibrous tissue interrupting or pressing on the bundle of His; such abnormalities have been found at necropsy (Lampard, 1928; Yater *et al.*, 1933; and Wallgren and Winblad, 1937). Brown (1950) points out that the most vulnerable part of the A-V bundle is where it passes in the posterior part of the endocardial canal between the endocardial cushions, and that abnormal ingrowth of the fibrous tissue of the annulus fibrosus might interrupt its course here.

Apart from the heart block, only Case 8 among our seven patients of Group I had evidence of any structural fault. Reasons have been given for thinking that he had developed aortic incompetence sometime after he was 20, possibly from pathological changes on congenital bicuspid aortic valves. Towers and Bremer (1947) have reported a case of supposed congenital aortic incompetence with complete heart block. The other six of our seven patients showed no evidence of ventricular septal defect or other congenital abnormality. One of the criteria of Yater for

accepting heart block as congenital, viz. other signs of congenital heart disease, should therefore be omitted, and all that is needed is recognition of the slow pulse at an early age before there is any history of diphtheria or of rheumatic fever.

The Association with Bundle-Branch Block. The occurrence of bundle-branch block with acquired heart block is not uncommon (Kay, 1948): Campbell (1944) for example found it in 19 out of 64 patients. The complication suggests extensive involvement of the conducting system, usually as a result of coronary disease, and carries a poor prognosis. Thus Katz (1941) maintained that the average expectation of life was " seldom longer than a year or two." In patients with congenital heart block, however, a bundle-branch block pattern appears to be uncommon, and Kay found it in only one out of twenty patients. Here, as in our Case 8, it was of the left bundle-branch type.

Variations in the Type and Degree of Heart Block. These changes seem to be more common in patients with acquired than with congenital block. Thus Ellis (1932) found that in his series of 43 patients the condition was acquired in the 3 who had intermittent complete block, while his 9 congenital cases showed no intermissions. Similarly all 12 cases of intermittent block of Butler and Levine (1930) were examples of the acquired condition. Nevertheless several congenital cases with altering block have been recorded. The patient of Waldman (1945) showed at different times prolongation of the P–R interval and complete A-V dissociation; the patient of Faessler (1939) showed sinus rhythm, A-V nodal rhythm, and complete block; and other examples are given in Table II.

Waldman suggested that there were two ways in which these variations could occur. An incomplete interruption of the conducting fibres could be rendered temporarily complete by increasing mechanical tension applied to the bundle; and here he cited the patient of Smith (1921) in whom normal sinus rhythm could be restored during forced expiration when the heart lay in a more horizontal position. Or a disturbance of the blood supply to the conducting system might produce a similar effect; and here he quoted Faessler's (1939) patient who was found at necropsy to have gross atheroma of the artery to the A-V node, besides other abnormalities. Whatever the cause of these variations, it is easier to understand why a patient with incomplete block should subsequently develop complete block (Clark and White, 1952) than why the reverse should happen, as it did in our Case 7.

Prognosis. Opinions on the prognosis of congenital complete heart block have varied. Yater *et al.* (1933) stated that " it should be considered serious in all cases since a major defect is probably always present " and Leech (1930) also thought the outlook unfavourable. Most workers (Taussig, 1947; White, 1951) take a more optimistic view, however, and a number of patients are known to have had the condition for long periods, 56 years (our Case 5), 40 years (our Case 2), 35 years (Benjamin and White, 1952), over 30 years (Smith, 1933), 28 years (Harris, 1929), 26 years (Clark and White, 1952), and 24 years (Butler and Levine, 1930; Ellis, 1932). The prognosis must depend on whether " a major developmental defect " is in fact present in most patients, and this question has been discussed. We think that the structural abnormality, when present is not so much a cause of the block as a parallel manifestation of deranged development. Langendorf and Pick (1954) also suggest that the responsible defect is in the bundle of His itself rather than a mechanical interruption of a normal bundle of His by the septal defect or other structural abnormality.

It should not be thought that the heart block itself is never of importance, for sudden death, due presumably to acute disturbances of cardiac rhythm, has been reported in these patients (Aylward, 1928; Aitken, 1932; Ellis, 1932; Clark and White, 1952). In general, however, we agree with Brown (1950) and in our opinion the prognosis is that of the associated lesion, if any, and the heart block itself is generally unimportant.

Summary and Conclusions

Seven patients with congenital complete block, who have been reported previously, have now been followed for twenty-five years and their progress and present condition are described. One

has died from an obscure cardiovascular condition, but the others are all doing well. When they were last reported the block had so far as was known been complete all the time but one has since developed sinus rhythm with latent heart block.

Only one has a large heart and evidence of an additional lesion, probably aortic incompetence. All the others have systolic murmurs that are thought to be functional or cardio-respiratory. None has a palpable systolic thrill or any good evidence of a ventricular septal defect, though this was suspected originally because of the systolic murmur.

Although the patients are growing older the heart rate is still faster than in acquired heart block, 40 to 50 instead of 28 to 40 a minute. The pulse pressure is generally somewhat widened, about 60 mm., but there is no tendency for the blood pressure to rise as the patients get older. Apart from the block the electrocardiogram is generally normal.

We are reporting also eight new patients with heart block and manifest congenital heart disease—three with Fallot's tetralogy (one of these with dextrocardia), one with Eisenmenger's complex, one with transposition of the main arteries, one perhaps with tricuspid atresia, and two with atrial septal defect. The first five of these have, of course, a ventricular septal defect as well as other congenital lesions. Here the heart block was less often complete and 2 : 1 block or latent block with dropped beats were sometimes seen. When the block was complete the ventricular rate was even faster than in the first group, generally between 50 and 70 a minute.

When there is an added structural abnormality, this is not as a rule the direct cause of the block, so much as a parallel disturbance of development. Sometimes the block is due to a fibrous interruption of the bundle of His.

In general, the prognosis is that of the associated lesion and it is not greatly affected by the presence of the heart block.

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DISABILITY AND CIRCULATORY CHANGES IN MITRAL STENOSIS

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Investigations associated with the surgical treatment of mitral stenosis have led to an increase in our understanding of the cause of disability in that condition. There are three reasons for this. First, the selection of cases for operation requires the separation of patients in whom operable mitral stenosis is the chief cause of disability, and this requirement has resulted in more exact diagnosis than was previously necessary. Secondly, judgment of the value of mitral valvotomy has led to a careful assessment of the degree of the patient's disability before and after the widening of the stenosed valve. Thirdly, the use of cardiac catheterization as a method of investigation has permitted measurement of the circulatory changes associated with the different degrees of disability.

These developments led to an investigation of the circulatory changes associated with different degrees of disability in patients with uncomplicated mitral stenosis. By showing the sequence of circulatory changes with increasing disability, and the degree of their reversal after successful mitral valvotomy, the investigation suggests which changes are more important in the causation of symptoms. The study also has a practical aspect, for it defines the pattern of circulatory changes to be expected with each grade of disability due to uncomplicated mitral stenosis. These patterns have been compared with those in patients in whom causes of disability in addition to mitral stenosis were present. The results of this comparison may be of assistance in determining whether mitral stenosis is the chief cause of disability when the exact assessment of a case is difficult.

Circulatory changes that might be the cause of symptoms in mitral stenosis have been demonstrated by many investigators. In 1923 Meakins *et al.* showed that the circulation rate is reduced and its increase on exercise is limited. Cournand (1947) found a marked increase in pulmonary artery pressure in some patients. Hellems *et al.* (1949) showed how to measure the increased pressure in the pulmonary capillaries. Gorlin and Gorlin (1951) suggested a method using hydrodynamic principles by which the decrease in the " area of the mitral valve opening " might be calculated. Epps and Adler (1953) measured the increase of pressure in the left atrium.

The relation of the degree of these changes in the circulation to the disability from which the patients suffered has also been the subject of considerable study. Borden *et al.* (1949) related disability to the elevation of the pulmonary arterial pressure and the reduction of cardiac output. Eliasch (1952) included measurement of the pulmonary capillary pressure in his comparison, and Dexter *et al.* (1952) calculated the " mitral valve area." The relief of disability following mitral valvotomy has been compared in individual patients with the corresponding change of circulatory measurements by Draper *et al.* (1951) and Donald *et al.* (1954). The findings in general were that with increased disability there was a greater departure from normal of circulatory measurements. However, it was not established which changes are more closely associated with disability. There are two reasons for this. The number of patients studied was not large enough to take individual differences into account, and the significance of the findings was reduced by the inclusion of patients showing evidence of lesions in addition to the mitral stenosis.

During the past six years we have made a study of the relationship between disability and circulatory changes in an experiment designed to define it as precisely as possible. A careful investigation of each patient enabled us to exclude those in whom causes of disability other than mitral

* Working on behalf of the Medical Research Council.

stenosis might exist, and to assign the selected patients to one of four groups according to the degree of their disability. The number of patients had to be large in order to take into account the individual variations to be expected in any group of patients. Statistical analysis of the findings ascertained which measurements showed the more significant differences between the groups of patients.

Material

Since 1948 more than a thousand patients with rheumatic heart disease have been referred to this hospital for mitral valvotomy, and cardiac catheterization has been carried out on more than 200 of these as an aid to determining their suitability for operation. In only 81 of these did we consider that mitral stenosis was the sole cause of their disability, though sometimes it was accompanied by atrial fibrillation. As will be shown later the inclusion of the latter patients had an insignificant effect on the conclusions reached. All the 81 patients had the long rumbling diastolic murmur typical of mitral stenosis. All came to operation, with the exception of four whose disability was judged too slight to justify mitral valvotomy, and at operation the clinical diagnosis was confirmed by direct observation. The following complications have been considered and excluded as factors contributing to their disability.

Aortic Valve Disease. No patient had a systolic murmur in the aortic area. In twelve patients a less than Grade II early diastolic murmur to the left of the sternum had been heard on occasions, but in none was there any alteration of the peripheral pulse, unusual pulsation in the left ventricle on fluoroscopy, or clinical, radiological, or electrocardiographic evidence of left ventricular hypertrophy to indicate that the murmur was due to aortic valve disease.

Mitral Incompetence. Four patients had a soft systolic murmur at the cardiac apex, but at valvotomy none of these patients had a valve orifice greater than 1·0 × 0·5 cm., and no regurgitant stream was felt. None of these patients had clinical, electrocardiographic, or radiological evidence of left ventricular hypertrophy.

Tricuspid Valve Disease. Nine patients had a soft systolic murmur medial to the apex or in the tricuspid area, but in none of these were there any other signs of tricuspid incompetence. Tricuspid stenosis was excluded because no patient had, at catheterization, a measurable pressure gradient across the tricuspid valve during diastole.

Hypertension. No patient had a systolic blood pressure higher than 140 mm. Hg, nor a diastolic pressure higher than 90 mm. Hg.

Respiratory Disease. No patient had clinical or radiological signs of emphysema, nor recurrent bronchitis antedating cardiac dyspnœa.

Active Rheumatism. No patient had pyrexia, a raised sedimentation rate, or recent arthralgia.

Anæmia. No patient had a hæmoglobin of less than 11 g. per 100 ml.

Cardiac Neurosis. We have excluded all patients in whom the possibility of the complication of cardiac neurosis was suspected.

There were 27 men and 54 women; 22 patients were in the third decade, 42 in the fourth decade, and 17 in the fifth decade. Twenty-five of the patients included had established atrial fibrillation with ventricular rate controlled by digitalis. At the time of catheterization no patient had clinical signs of congestive heart failure; in none was the right atrial mean pressure higher than 10 mm. Hg. Twenty-seven of these patients were studied again after mitral valvotomy, from which operation 23 had derived much relief and four less relief. The findings provide the opportunity to observe which changes in measurement accompany the relief of symptoms.

Methods

The patient's degree of disability in his everyday life was determined from a detailed history, according to the following scheme.

Grade A No disability. 0 patients.
Grade B Unduly breathless on walking quickly on the level or walking at normal pace up an incline. 7 patients.
Grade C Breathless on moderate exertion and unable to hurry, though able to walk some miles on the level at their own speed. 18 patients.
Grade D Unable to walk more than a few hundred yards because of dyspnœa and fatigue, and forced to take frequent rests on inclines or stairs. Seriously incapacitated in day to day activity, and unable to do more than light work. 37 patients.
Grade E Breathless and fatigued on very light activity and usually confined to their homes. 19 patients.

For the assessment of disability we had the advantage of consultation with the physicians under whose care the patients were, Dr. Maurice Campbell and Dr. Charles Baker. Either Dr. Campbell or Dr. Baker first saw the patient and made an assessment of disability. Our independent assessment usually agreed with theirs, and never differed by more than one grade of disability; agreement was reached by discussion of the case. Each assessment of disability therefore is the agreed view of two or three physicians.

Cardiac catheterization was done a day or two after the clinical examination. To minimize emotional disturbance at catheterization this interval was used to gain the confidence of the patient. The day before catheterization he was taken to the room in which the catheterization was to be performed and given practice in breathing through the spirometer. The procedure to be adopted was explained to him as clearly as possible, taking care not to frighten him. During actual catheterization care was taken to keep physical discomfort to a minimum. The patient lay supine on the couch which was inclined at 15 degrees to the horizontal so that his head was slightly raised. When necessary, an orthopnœic patient was supported by additional pillows.

Pressures were measured by electronic capacitance manometers (Peterson *et al.*, 1949). All pressures were referred to the intersection of the mid-sagittal and mid-coronal sections at the level of the fourth costal cartilage.

The precautions taken in recording " pulmonary capillary pressure " have been described elsewhere (Venner and Holling, 1953). A double lumen catheter was used to measure pulmonary artery and capillary pressures simultaneously. When necessary mean pressures were determined by planimetry from the records.

Oxygen consumption was measured by a spirometer fitted with thin rubber flap valves to reduce resistance. In the earlier observations oxygen was breathed from the spirometer; later the apparatus was modified so that air or oxygen could be breathed (Donald and Christie, 1949). Breathing oxygen has the effect of raising the oxygen saturation of arterial and venous blood an average of 5 per cent, without altering the arterio-venous oxygen difference. In a few early cases observations on the mixed venous blood were obtained only whilst the patient was breathing oxygen; when necessary for comparative purposes these were corrected by the subtraction of 5 per cent. Brachial artery and pulmonary arterial samples were taken for the estimation of the A-V oxygen difference. The samples were kept in iced water and analysed as soon as possible, that is within 2 to 3 hours. The Haldane blood gas apparatus was used to determine the oxygen saturation of the samples (Douglas and Priestley, 1948). The accuracy of this method has been considered fully elsewhere (Holling *et al.*, 1955). The total oxygen combining power was determined indirectly by colorimetric estimation of the hæmoglobin content (Reeve, 1944). The cardiac output was calculated using the Fick principle. To enable comparisons to be made between patients of different physique, the cardiac output is expressed as the cardiac index in litres per minute per square metre of body surface area.

At catheterization the response to exercise was observed as the patient pedalled against a spring resistance at the rate of one leg extension per second, timed by a metronome. The rate of working was 1/70 H.P. and was maintained at a steady rate for at least five minutes. The rate of oxygen consumption was at least doubled. Blood samples were taken and pressures measured during the last minute of exercise. Severely disabled patients were not exercised.

At valvotomy the pressure in the left atrium, right and left ventricles, pulmonary artery, and aorta was measured through a 21-gauge needle connected with a manometer by a metre of hardened plastic tubing of 1·4 mm. diameter bore.

Because patients continued to improve for some months after valvotomy and changes in the circulatory state take place over this time (Baker *et al.*, 1952), at least six months were allowed to elapse between operation and recatheterization. In the majority of patients this interval was about a year, the longest interval being four years.

The size of the mitral valve orifice was estimated by the surgeon at operation and was also calculated from a formula (Gorlin and Gorlin, 1951).

The ratio

$$\frac{\text{mean pulmonary artery pressure} - \text{mean pulmonary capillary pressure (mm. Hg)}}{\text{cardiac output (litres per minute)}}$$

which has been claimed to measure the pulmonary vascular resistance, was calculated for rest and exercise in each patient where this was possible. The results are expressed in arbitrary units of resistance. The vital capacity was measured in most patients before and after valvotomy.

In the statistical analysis of results the patients have been treated as groups according to the degree of their disability. For each circulatory measurement the mean value for each group of patients was calculated. All measurements showed a greater departure from normal in the more seriously affected patients, but the significance of the differences found between groups differed according to the measurement. In order to estimate the significance of these differences due allowance must be made for the variation of

findings in each group, and for the fact that, for various reasons, all measurements could not be made on all patients. "Student's" t test was applied to the results.*

RESULTS

The results obtained in the 81 patients with mitral stenosis are given in Tables I—V.

TABLE I

DISABILITY AND CIRCULATORY CHANGES IN MITRAL STENOSIS AT REST (R) AND ON EXERCISE (E) (81 PATIENTS)

		Grade B disability (7 patients)		Grade C disability (18 patients)		Grade D disability (37 patients)		Grade E disability (19 patients)	
		No. of cases	Mean and S.D.	No. of cases	Mean and S.D.	No. of cases	Mean and S.D.	No. of cases	Mean and S.D.
Mitral valve area, sq. cm.	R.	6	1·97± 0·72	16	0·94± 0·28	26	0·85± 0·34	6	0·52± 0·10
	E.	5	1·87± 1·0	9	1·10± 0·19	10	0·76± 0·25	1	0·45± —
Cardiac index, litres/sq.m./min.	R.	6	2·77± 0·5	18	2·31± 0·5	37	2·28± 0·5	19	1·98± 0·7
	E.	5	3·76± 1·3	17	3·02± 0·8	29	2·83 ± 0·9	11	2·31± 0·7
Stroke index, ml.	R.	4	34·0 ±10·3	15	29·6 ± 8·0	30	27·0 ± 7·2	9	22·0 ± 7·3
	E.	3	30·3 ± 7·3	14	29·6 ±13·5	23	23·0 ± 8·4	7	17·5 ± 5·5
Oxygen saturation of mixed venous blood (%)	R.	7	69·0 ± 3·0	18	65·0 ± 7·0	37	58·0 ± 7·9	19	49·0 ± 9·0
	E.	5	55·0 ± 6·0	17	52·0 ± 9·0	31	42·0 ±10·0	13	32·0 ±10·0
Left atrial mean pressure (at operation), mm. Hg	R.	2	12·5 —	12	23·0 ± 5·0	32	28·0 ± 8·0	9	26·0 ± 6·0
	E.	–	— —	–	— —	–	— —	–	— —
Pulmonary capillary mean pressure, mm. Hg	R.	7	11·0 ± 4·0	17	22·0 ± 6·1	26	23·0 ± 7·9	7	25·0 ±12·3
	E.	5	20·0 ± 8·0	9	25·0 ± 9·7	9	35·0 ± 7·7	1	35·0 ± —
Pulmonary arterial mean pressure, mm. Hg	R.	7	18·0 ± 5·0	18	33·0 ±10·0	34	51·0 ±17·0	18	65·0 ±19·0
	E.	5	26·0 ± 9·0	16	46·0 ±18·0	27	74·0 ±26·0	13	91·0 ±19·0
Pulmonary arterial resistance, units	R.	7	1·5 ± 0·76	17	3·0 ± 2·44	27	7·6 ± 5·27	6	13·3 ± 9·02
	E.	3	1·2 ± 0·61	9	3·8 ± 2·6	10	11·4 ± 7·7	2	31·0 ± 7·9
Vital capacity, litres/sq. m.	R.	7	1·4 ± 0·3	14	1·4 ± 0·2	36	1·3 ± 0·2	15	1·2 ± 0·3

DISCUSSION

Reliability of Findings. Before making any comparison of disability and objective measurement it is important to consider the reliability of both. In the final assessment of a patient's condition it is possible to be more impressed by the seeming accuracy of a laboratory measurement than by comparatively indefinite clinical judgment.

It is recognized that various factors affect the disability caused by a cardiac lesion. For example, one patient will be brought to a stop by a degree of dyspnœa that another will ignore.

* The significance of any difference found is shown by the value "p" which expresses the probability that the observed difference was due to chance. The smaller the value of p, the less likely is the difference due to chance. A p value of 0·05 or less has been accepted as significant, and indicates that the probability of the difference being due to chance is less than 1 in 20; a p value of 0·005 or less has been accepted as highly significant, and indicates that the probability is less than 1 in 200. Obviously, any measurement that shows significant differences between adjacent pairs of groups B and C, C and D, D and E, will be of more value as an objective measure of the patient's condition than one that shows less significant differences.

TABLE II

COMPARISON OF FINDINGS IN PATIENTS WITH NORMAL RHYTHM AND THOSE WITH ATRIAL FIBRILLATION

Disability group	At rest				During exercise			
	Normal rhythm		Atrial fibrillation		Normal rhythm		Atrial fibrillation	
	No. of patients	Mean	No. of patients	Mean	No. of patients	Mean	No. of patients	Mean
Pulmonary artery mean pressure in mm. Hg								
B	6	17	1	22	5	26	1	45
C	11	32	6	33	10	53	6	57
D	25	51	8	48	21	76	6	71
E	11	59	7	63	9	95	4	83
Pulmonary capillary mean pressure in mm. Hg								
B	6	11	1	16	4	17	—	—
C	11	22	6	21	6	27	3	28
D	20	24	7	24	9	38	1	27
E	4	28	3	31	1	42	1	35
Cardiac Index in litres/sq.m./min.								
B	5	2·9	1	2·2	4	4·0	1	3·0
C	12	2·6	6	1·9	11	3·3	6	2·5
D	26	2·3	11	2·2	22	3·0	7	2·5
E	12	1·9	7	1·8	8	2·5	3	1·7
Mixed venous blood in % saturation								
B	6	68·6	1	71	5	55	—	—
C	12	67·7	6	58·7	11	54	6	48
D	26	59·2	11	49·3	22	43	8	37
E	12	45·6	6	49·8	10	33	3	31

TABLE III

P VALUE OF DIFFERENCE OF MEAN FINDINGS, GROUP BY GROUP

	Grades B and C		Grades C and D		Grades D and E	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Mitral valve area	0·63	0·04	0·40	0·005	0·45	—
Cardiac index	0·08	0·12	0·80	0·55	0·07	0·08
,, ,, (patients in sinus rhythm) ..	0·2	0·3	0·2	0·3	0·05	0·3
Stroke index	0·40	1·00	0·30	0·08	0·02	0·10
Oxygen saturation (percentage) of mixed venous blood	0·15	0·27	0·001	0·005	0·001	0·005
Left atrial mean pressure	0·02	—	0·05	—	0·70	—
Pulmonary capillary mean pressure ..	0·02	0·35	0·65	0·08	0·60	—
Pulmonary arterial mean pressure	0·001	0·03	0·001	0·001	0·01	0·02
Pulmonary arterial resistance	0·15	0·10	0·10	0·01	0·10	0·01

Significant differences underlined. Highly significant differences doubly underlined.

TABLE IV

Findings Before and After Mitral Valvotomy

Patients Grouped According to Degree of Clinical Improvement after Operation

Case No.	Improvement in clinical grading		Blood oxygen combining power (ml./100 ml.)		Arterial blood (O_2 % satn.)		Mixed venous blood (O_2% satn.)				Vital capacity (litres/sq.m.)		Pulmonary artery mean pressure (mm. Hg)				Pulmonary capillary mean pressure (mm. Hg)				Cardiac output (litres/min.)				Stroke volume (ml./beat)			
							Rest		Exercise				Rest		Exercise		Rest		Exercise		Rest		Exercise		Rest		Exercise	
	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.
							Mitral stenosis.				*Normal rhythm.*		*Great improvement*															
G 6	E	B	17·0	18·0	91	99	44	58	19	45	—	—	100	32	116	60	—	14	—	29	2·7	3·8	2·7	4·0	—	37	—	32
G 43	E	B	18·7	19·0	96	99	47	68	—	56	1·2	1·2	80	30	—	36	—	9	—	—	2·4	4·0	—	5·4	—	73	—	67
G 42	E	B	20·4	20·5	95	95	58	62	39	48	1·5	1·5	44	30	92	77	26	8	—	—	3·0	3·6	3·1	4·5	40	51	28	50
G 31	E	B	20·1	24·0	93	92	42	65	35	62	1·1	1·3	53	23	104	44	27	9	—	24	2·6	3·5	4·6	5·2	36	41	41	60
G 9	E	B	14·4	20·8	96	95	47	56	32	45	1·5	1·6	52	35	75	44	—	26	—	32	2·7	2·8	4·5	4·3	—	39	—	55
G 10	E	B	15·8	21·5	86	95	52	65	—	61	—	1·0	71	32	115	36	—	—	—	—	3·5	3·2	—	3·8	—	29	—	29
G 55	E	B	17·0	19·0	95	95	30	66	34	53	1·5	—	83	35	115	57	29	11	42	19	2·4	4·2	2·9	6·1	25	51	26	61
G 52	D	B	17·7	18·4	92	97	55	66	44	41	1·4	—	50	28	70	44	—	18	—	33	2·7	3·2	5·5	4·5	28	47	42	53
G 13	D	B	15·4	18·8	92	98	64	66	44	60	—	—	77	28	115	54	—	6	—	14	5·5	5·5	7·5	7·0	—	78	—	67
G 35	D	B	17·8	17·9	97	98	55	70	30	65	1·6	1·5	49	31	74	43	17	18	—	26	3·2	4·3	5·3	6·1	35	60	35	73
G 38	D	B	14·1	22·8	92	96	58	73	52	71	1·5	1·4	35	27	62	58	20	17	—	38	3·9	4·9	7·8	7·4	76	66	87	80
G 22	D	B	16·4	16·9	95	—	60	60	49	63	0·95	1·0	34	16	54	27	22	10	—	16	4·3	4·1	7·5	6·2	—	68	—	89
G 8	D	B	16·8	18·9	77	94	25	63	—	54	—	1·6	85	24	—	42	—	—	—	—	3·2	3·9	—	4·4	—	67	—	52
G 32	D	B	18·7	23·5	94	95	60	64	—	63	1·5	1·6	41	20	—	25	30	16	—	—	4·0	4·0	—	5·6	57	50	—	56
G 46	D	B	16·4	16·6	94	95	55	70	—	57	1·6	—	60	20	—	30	32	8	—	15	2·3	4·3	—	5·5	28	50	—	60
G 73	D	B	20·2	20·2	96	99	68	67	60	64	—	—	30	19	40	24	19	12	28	17	3·2	3·5	4·6	5·6	49	52	70	67
G 84	D	B	16·4	16·7	94	95	59	75	55	57	1·4	—	36	18	42	45	26	12	—	26	3·4	5·6	3·6	6·6	52	78	50	75
Mean change			+ 2·2		+ 3·6		+ 13·9		+ 13·4		+ 0·05		− 31·3		− 35·5		− 12·7				+ 0·8		+ 1·0		+ 14·0		+ 18·5	
S.D.			± 0·7		± 1·18		± 2·7		± 2·77				± 4·5		± 7·0		± 2·58				± 0·23		± 0·25		± 4·23		± 5·19	
							Mitral stenosis.				*Atrial fibrillation.*		*Great improvement*															
G 5	E	B	21·2	23·5	95	95	54	65	—	60	1·4	1·4	51	22	70	42	—	10	—	—	4·3	3·9	—	6·0	—	—	—	—
G 29	E	B	20·6	21·0	92	96	48	62	34	49	1·4	1·3	84	23	122	47	29	11	35	28	2·9	2·6	2·3	3·5	36	43	—	41
G 27	D	B	17·8	17·2	—	94	62	58	—	46	1·3	1·7	57	37	—	52	21	12	—	—	4·8	3·2	—	3·5	53	58	—	45
G 23	D	B	17·5	21·5	91	—	60	60	34	—	1·7	1·7	20	17	57	—	12	—	—	—	5·5	4·0	5·7	—	73	70	57	—
G 44	D	B	19·0	18·5	81	96	53	62	35	55	1·3	1·1	53	30	96	55	24	16	—	22	2·6	2·9	2·2	2·7	25	32	15	27
G 59	D	B	21·4	22·8	92	96	55	60	39	54	1·3	—	88	30	124	50	—	9	—	15	3·1	3·4	2·9	5·3	39	55	21	68
Mean change			+ 1·5		+ 5·0		+ 5·8		+ 16				− 31		− 54		− 12				− 0·53		+ 1·4		+ 6·2		+ 30	
S.D.			± 0·3										± 0·2															
							Mitral stenosis.				*Moderate improvement*																	
G 39	E	C	18·4	20·6	—	98	50	66	—	51	1·0	1·3	56	26	—	33	30	16	—	22	2·7	2·7	—	2·9	34	31	—	25
G 4	E	C	16·0	17·6	95	94	54	64	—	—	—	—	40	27	—	—	—	—	—	—	2·5	3·3	—	—	31	39	—	—
G 24	E	D	17·4	17·8	94	—	43	60	31	45	1·3	1·3	—	67	—	79	—	38	—	—	2·9	3·0	3·4	3·6	35	37	32	38
G 58	C	B	17·0	18·0	93	93	58	70	49	53	—	—	35	18	70	30	25	8	30	19	3·8	5·7	5·9	—	63	81	69	—
Mean change			+1·3				+ 14		+ 9				− 20				− 15				+ 0·7				+ 6			

Columns headed B show observations made before mitral valvotomy, columns headed A contain observations made after valvotomy.

TABLE V

CALCULATED MITRAL VALVE AREA (SQ. CM.) BEFORE AND AFTER OPERATION

Case	Before operation		After operation	
	Rest	Exercise	Rest	Exercise
Mitral stenosis. Good result. Normal rhythm				
G 42	0·6	—	1·9	—
G 31	0·5	—	1·7	1·2
G 55	0·5	0·5	1·7	1·7
G 35	0·8	—	1·1	1·1
G 38	0·8	—	1·2	1·3
G 22	1·0	—	1·5	1·6
G 32	0·7	—	1·1	—
G 46	0·4	—	2·4	1·7
G 73	0·8	0·8	1·2	1·6
G 84	0·7	—	2·3	1·4
Mitral stenosis. Good result. Atrial fibrillation				
G 29	0·5	0·5	0·9	0·7
G 27	1·1	—	1·0	—
G 44	0·6	—	0·8	0·7
Mitral stenosis. Moderate result				
G 39	0·5	—	0·8	0·8
G 58	0·7	1·1	1·0	—

The history is influenced by the patient's memory and intelligence, and by his desire to have, or to avoid, an operation ; after operation his symptoms may be affected by factors other than the physical improvement due to valvotomy. These considerations indicate the care with which a patient's statements must be judged. Further, although it is expedient to classify the patients into five groups, disability shows continuous graduation, so that some of the patients might have been put into an adjacent group. For these reasons it had been questioned whether a patient's disability can be assessed accurately from his symptoms ; but with the care we took over this, we believe that the grading was reasonably accurate. Moreover, since the object of treatment is to relieve disability rather than to alter laboratory findings, unless it can be shown that the two are related it is more practical to use disability as a measure of the patient's general condition than to use the result of a laboratory observation.

The reliability of laboratory findings is also difficult to assess. The technique of the actual measurement may be accurate, but the findings may be unreliable because we might have failed to achieve a basal or steady state in the patient during observations. Cardiac catheterization is likely to be a disturbing procedure for the patient and in spite of all precautions it may not be possible to observe him in a basal state. The degree of emotional disturbance may be difficult to assess, for we have observed some elevation of the pulse rate and oxygen consumption in an apparently tranquil patient. Patients in whom the degree of disturbance was such that the pulse rate was over 100 a minute have been excluded from this series. In early observations it was found that the supine position during catheterization sometimes caused distress, with a rise of the pressure in the pulmonary vessels and a reduction in arterial oxygen content : the results obtained from these patients have also been discarded. Furthermore, painful or emotional stimuli may cause a rise of pulmonary vascular pressures. Thus, while we acknowledge that the possibility exists that observations were made in some patients who were not basal, we made every effort to recognize and minimize abnormal conditions. If we had any grounds for doubt in this respect we have not included the results in this series.

The technical error of a single measurement may or may not be great, but when a number of measurements are combined, as in calculation of the cardiac output or of the mitral valve area, the error of the final figure is a function of all the measurements used in its calculation. For this reason,

direct measurements are more to be relied on, for example the oxygen saturation of the mixed venous blood as an indication of the adequacy of the blood flow to the needs of the body, rather than the calculated figure for the cardiac output. Originally we mistrusted the figures obtained when the " area of the mitral valve " is calculated, because the calculation is based on five measurements and three assumed figures. We compared the figures obtained in the resting patients with that in the same patients when exercising, and if the calculated area is related to the true area the two results should correspond. Our mistrust of the values obtained lessened when it was found that the two series of results corresponded well, though exceptions occurred ; i.e. G 58, 46, and 84 (Table V). These findings are in agreement with those of Gorlin and Gorlin (1951) and also of Rodrigo (1953) who, on theoretical grounds, assessed the likely error in the calculation of the mitral valve area to be about 20 per cent.

As will be seen later, we were able to show a significant, sometimes highly significant, relationship between our assessment of the degree of disability of a group of patients and certain of the laboratory findings. We conclude therefore that clinical assessment of disability and certain laboratory findings support and justify each other as measurements of the severity of the disease.

Relationship of Disability to the Measurements Made

Mitral Valve Area. If the symptoms in patients with mitral stenosis are either the direct or indirect result of obstruction caused by the stenosed valve, the degree of stenosis should be related to the degree of disability. We find that once symptoms become noticeable (Grade B disability) the calculated mitral valve area is already reduced to less than half the area of the healthy valve. A large difference in valve area occurs between patients with only slight disability (Grade B), and those with more, though still only mild symptoms (Grade C), the mean valve area of the former being twice that of the latter (Table I). With increase in disability the mean value of the mitral valve area calculated for each group is successively smaller. Statistical analysis of the differences found shows (Table III) that those between disability grades B and C, and C and D are significant if the figures obtained during exercise are used, but since so few patients of Grade E disability were allowed to exercise it was not possible to obtain sufficient data to discriminate between Grades D and E.

Though the mean calculated mitral valve area does show a change between the grades, it is to be noted that the changes are slight, and it seems to us unlikely that the surgeon at operation could appreciate such fine differences. Indeed the valve areas in these patients were reported by the surgeon as relatively constant from patient to patient (Brock, 1952).

In 15 of the patients it was possible to compare the calculated mitral valve area before and after mitral valvotomy (Table V). In general the results are consistent with the clinical state of the patient. Ten patients in normal rhythm who derived great benefit from operation showed an increase in mitral valve area to more than a square centimetre. In three patients in atrial fibrillation who also derived great benefit from operation, the increase in calculated mitral valve area was less. It was also less in two patients who derived only moderate benefit from operation.

The calculated valve area of groups of patients with different degrees of disability can therefore discriminate between them. This suggests that the calculated mitral valve area is related to the actual mitral valve area, and that disability may be related to the degree of stenosis.

Anomalous results of this calculation, however, are sometimes obtained, and since small differences in mitral valve area appear to have a large effect on disability, greater precision in its measurement should be sought. More reliable figures for its calculation might be obtained if the pressure gradient across the valve during the filling time of the left ventricle could be measured directly. This could be done at operation or by puncture of the left atrium (Epps and Adler, 1953) and passing a fine catheter from left atrium through the mitral valve so that the pressure on each side of it could be measured. A simultaneous measurement of the mitral valve flow would have to be made to calculate the mitral valve area. These measurements are possible and would be of considerable theoretical interest as providing a measure of the degree of narrowing of the mitral

valve, and would be of practical use to the surgeon as a measure of the technical success of his operation.

Cardiac Output. The calculated mitral valve area provides an index of the anatomical severity of mitral stenosis. A functional measure of the stenosis is given by the reduced blood flow through it. This is the cardiac output and, on theoretical grounds, the measurement is to be preferred to the calculation of the mitral valve area because it involves fewer assumptions.

Uncomplicated mitral stenosis of sufficient degree to give rise to symptoms always has the effect of reducing the cardiac output. Even in the group with least symptoms the mean cardiac output is less than normal (3·2 litres per sq. metre of body surface per minute). In groups of patients with greater disability, a slight further reduction of cardiac output is found with increasing disability (Table I). Whatever the disability, the increase of cardiac output on exercise is small. It is progressively smaller from Grade B to Grade E.

Though these changes occur, relationship between the degree of disability and the degree of reduction of cardiac output is not a close one. Neither cardiac output nor the lessened ability to increase the cardiac output on exercise affords a sensitive means of distinguishing between disability groups (Table III). The changes in cardiac output after valvotomy also indicate that the level of cardiac output is not closely related to the degree of disability. Thus a group of 17 patients in sinus rhythm showed an insignificant increase in cardiac output after operation, whereas a group of six with atrial fibrillation showed an insignificant decrease. The ability to increase cardiac output on exercise showed no alteration in the group of patients with normal rhythm ; and a greater increase in the three patients with atrial fibrillation than before operation. Yet all these patients had derived similar and great improvement as a result of the operation.

The poor relation of disability to our measurements of restriction of cardiac output is surprising. It may be because expression of the cardiac output in terms of flow per minute is an inadequate measure of restriction of the circulation. To express the results in terms of stroke volume might be more satisfactory, especially when dealing with the effects of exercise, because shortening of the ventricular filling time during the tachycardia of exercise (Wiggers, 1923) exaggerates the obstructive effect of mitral stenosis. The results in Table I show that the stroke volume usually falls during the tachycardia of exercise, even in the most mildly affected groups. Often the reduction in stroke volume is sufficiently great to account for a reduction of cardiac output measured over a minute, particularly in the more severely affected patients. This confirms the opinion that tachycardia is an inefficient method of increasing cardiac output in the presence of mitral stenosis. A decided increase in stroke volume is often, but not invariably, seen following a successful valvotomy. The measurements of stroke volume as a whole, however, are too variable (Table III) to serve as a method of discrimination between groups of patients with different degrees of disability.

Oxygen Saturation of the Mixed Venous Blood. This indicates the effectiveness of the blood stream in supplying the needs of the body for oxygen. We have found it to discriminate between the groups of patients with different degrees of disability more decisively than the cardiac output (Table III). In the group with least symptoms the level is slightly less than in normal subjects, and decreases with increasing disability of the group (Fig. 1). After operation good clinical results are associated with a large increase in the oxygen saturation of the mixed venous blood though the patients with moderate improvement show a similar change (Table IV).

The effect of exercise on the oxygen saturation of the mixed venous blood of a normal subject has been reported to be only slightly altered by mild exercise (Hickman and Cargill, 1948), and Donald *et al.* (1955) found it to be reduced from a level of 79 to 69 per cent in four normal subjects performing exercise comparable in severity to that performed by our patients. When our patients with mitral stenosis exercised, the greater the degree of disability, the lower was the oxygen saturation of the mixed venous blood (Fig. 1 and Table I). The discrimination between the two groups of patients with mild symptoms was not significant (Grades B and C), but highly significant differences were found between disability grades C and D, and D and E (Table III). After operation the increase in oxygen saturation of the mixed venous blood on exercise was related to the degree of

improvement (Table IV), it even rose in some patients in the absence of an increase in cardiac output.

Oxygen saturation of the mixed venous blood discriminates better between the different degrees of disability than the cardiac output because cardiac output is but one of the factors affecting the carriage of oxygen to the tissues. Williams (1953) has shown that the oxygenation of the blood in the lungs may be impaired in mitral stenosis, and a reversal of this process is indicated by the increase in arterial oxygen saturation seen in many of our patients following operation (Table IV). We have also observed a rise in blood hæmoglobin content after a successful valvotomy (Table IV) showing that a diminished oxygen-carrying capacity of the blood was adding to the circulatory difficulties of these patients before operation.

The lowered oxygen content of the mixed venous blood seen in disabled patients is evidence of a threefold difficulty of oxygen supply, (1) reduced cardiac output, (2) reduced arterial oxygen content, (3) reduced oxygen-carrying capacity of the blood. The difficulty in oxygen supply is compensated for by an increased uptake of oxygen from each volume of blood passing through the tissues. Measurements of the oxygen saturation of the mixed venous blood can therefore be regarded as a comprehensive measure of the factors impeding the supply of oxygen to the tissues. As an objective measure of disability it is superior to, and has an additional advantage over, the cardiac output because it is a direct measurement and not derived from a calculation involving two other estimations—arterial oxygen content and the rate of oxygen consumption.

Left Atrial Pressure and Pulmonary Capillary Pressure. Another method that might gauge the severity of mitral stenosis is measurement of the rise of pressure behind it in the left atrium. This pressure has been measured directly at operation and also studied indirectly, but under more physiological conditions, as the pulmonary capillary pressure at catheterization. Epps and Adler (1953) showed that the pulmonary capillary pressure corresponded to the left atrial pressure, and our results agree with this in that the mean left atrial pressure of each group of patients is similar to the mean pulmonary capillary pressure (Table I).

In patients with Grade B disability the pulmonary capillary pressure is slightly higher than in normal subjects. The greatest and only significant (Table III) difference in pressure occurs between the mean pressure of this group with minimal symptoms and patients with definite, though still slight, symptoms (Grade C) (Fig. 2 and Table I). This corresponds to our finding of a difference in the calculated mitral valve area between the two mildly affected groups of patients and shows that, as the mitral valve narrows, a marked rise of pressure takes place behind it. In the absence of this increase of pressure gradient across the valve the difference in cardiac output between the groups of patients with Grade B and Grade C disability would be greater than that observed. The level of cardiac output therefore may be maintained by the increase of the pressure gradient. In the other groups of patients the increase in disability appears to be disproportionate to the small additional increases of pulmonary capillary and left atrial pressures. The mean pulmonary capillary pressure of the group of patients who are breathless on only moderate exertion (Grade C) being 22 to 23 mm. Hg, that of patients who are so disabled as to be confined to their homes being 25 to 26 mm. Hg. It is unlikely that our methods of measurement can discriminate between such fine differences, nor are the differences found significant (Table III).

Following valvotomy a fall in pulmonary capillary pressure from the range of 20 to 30 mm. Hg to the range of 10 to 20 mm. Hg is often observed in patients who are much improved, but over the whole series the fall after operation did not correspond well with the relief from disability. In a few patients in whom a low pulmonary capillary pressure was associated with severe symptoms before operation, considerable relief from symptoms was associated with only a small fall of pressure. The fall in two patients who derived only moderate benefit from operation was as much as in those who derived great benefit.

All patients showed a rise of pulmonary capillary pressure on exercise, and particularly high levels were reached in the patients who were more disabled (Table I and Fig. 2). However, the level of the pulmonary capillary pressure on exercise failed to provide a satisfactory means of discriminating between the groups of patients with different disability (Table III).

Pulmonary Artery Pressure. Previous work has established that slight increase of pulmonary capillary pressure in patients with mitral stenosis is associated with a comparable rise in pulmonary artery pressure, but that when the pulmonary capillary pressure is increased to about 25 mm. Hg a disproportionate rise of pulmonary artery pressure occurs (Gorlin *et al.*, 1951). Our observations show that the rise of pulmonary artery pressure is associated with an increase in disability. In the group of patients with minimal symptoms the pulmonary pressure at rest was slightly above normal (Table I and Fig. 2) and with greater disability a further rise of pressure occurs. Through all degrees of disability the mean pulmonary artery pressure of the group is found to bear a significant relationship to the degree of disability (Table III). This is apparent both in the observations made on the patients at rest and when they are exercising.

After valvotomy clinical improvement is associated with reduction of the pulmonary artery pressure both at rest and on exercise (Table IV). A large reduction in pulmonary artery pressure is always associated with much clinical improvement. Obviously in patients, in whom the pulmonary artery pressure is not greatly increased before operation, the fall in pressure is limited, though clinical improvement may be considerable. The degree of reduction of pulmonary artery pressure is less in patients who derive only moderate benefit from operation. Our finding that the elevation of the pulmonary artery pressure at rest and during exercise is more closely related to the patient's disability than the reduction in cardiac output does not agree with the opinion of Wade *et al.* (1954). It is questionable whether their material is sufficient on which to base an opinion, for findings in individual patients may differ from those of a more representative group : in seven only of the patients they investigated before and after mitral valvotomy was the lesion of mitral stenosis uncomplicated by other conditions, and according to our standards, marked clinical improvement occurred in only three of them after valvotomy. These three patients showed a fall in pulmonary artery pressure and a rise in cardiac output consistent with the observations in certain of our patients, e.g. G 55, G 6, and G 42 in Table IV, but the changes observed in these cases taken alone, show a different trend from the findings in the larger group of which they are a part.

Pulmonary Arteriolar Resistance and Disability. Since the rise in pulmonary artery pressure that occurs with increasing disability is not associated with an equal rise in pulmonary capillary pressure, it must be caused by an increase in the resistance of the pulmonary arterioles to the flow of blood through them. An indication of this resistance is given by the ratio,

$$\frac{\text{mean pulmonary artery pressure} - \text{mean pulmonary capillary pressure}}{\text{cardiac output}}$$

This was found to increase with increased disability (Table I). During exercise in the less severely affected patients it was unaltered, but in the more severely affected it rose. We find, however, that the calculated ratio gives a less close correspondence with the degree of disability than the simple pulmonary artery pressure (Table III). This is because the ratio includes the figures for the cardiac output and the pulmonary capillary pressure which are not closely related to the degree of disability. Moreover, for reasons we have stated in the analysis of results, a simple measurement is likely to be more reliable than a combination of readings.

Vital Capacity. In the observations made before operation there was little relation between the vital capacity and disability, and this measurement showed no significant change after mitral valvotomy, the mean increase in patients with a good clinical result being 0·07 litres per sq. metre of body surface area. It was our impression that the vital capacity was more related to the physique and previous mode of life of the patient than his disability.

Effect of Atrial Fibrillation. In this investigation, patients in normal rhythm have been considered together with patients with atrial fibrillation whose ventricular rate was controlled by digitalis. Since the relation between disability and circulatory measurements in patients with mitral stenosis might be altered by the onset of atrial fibrillation, it is necessary to enquire whether separation of the findings in patients with atrial fibrillation would have resulted in the relationship between

disability and circulatory measurements being more clearly defined. Whether the presence of atrial fibrillation causes an increase in disability is not relevant to this discussion.

In Table II, dealing with the observations made before operation, the patients with sinus rhythm have been separated from those with atrial fibrillation. From the results before and after operation shown in Table IV further comparisons between the two categories of patients may be made.

It is clear that atrial fibrillation does not affect the relation between disability and pulmonary vascular pressures. In the observations made before operation (Table II) no difference of pulmonary arterial and capillary pressures was found between the two categories of patients. The fall in pulmonary artery and pulmonary capillary pressure after a successful operation was similar, and the degree of improvement of symptoms was the same (Table IV).

The relation between disability and cardiac output is, however, affected when there is atrial fibrillation. Patients with fibrillation have a low and fixed cardiac output whether they are mildly or severely disabled ; those in normal rhythm show a reduction of cardiac output with increase of disability. Nevertheless, if patients with atrial fibrillation are separated, the measurements of cardiac output in those in normal rhythm still fail to show significant differences between groups of patients with different degrees of disability (Table III). After a successful operation there is an insignificant increase in the mean cardiac output of the patients with normal rhythm, and an insignificant decrease in those patients with atrial fibrillation.

No difference is found between the oxygen saturation of the mixed venous blood at rest in patients with normal rhythm and those with atrial fibrillation. On exercise the oxygen saturation of the mixed venous blood falls lower in the patients with fibrillation with Grades C and D disability, but no difference is found in the most severely affected patients. None of the differences were statistically significant.

These findings indicate that the relationship between disability and circulatory measurements is essentially the same in patients with normal rhythm and patients with controlled atrial fibrillation; only in the case of the cardiac output can minor differences be shown. It is therefore unlikely that consideration of the two categories of patients together has obscured the relationship between disability and circulatory measurements.

Circulatory Changes and the Development of Disability in Mitral Stenosis

If we assume that the calculated mitral valve area does in fact provide an approximate index to the size of the mitral opening then we can trace the sequence of circulatory changes in the average patient with mitral stenosis, as his disability increases with the progress of his disease (Fig. 1 and 2).

Stage I. Reduction of calculated size of " mitral orifice " from 4 to 6 sq. cm. to 2 sq. cm., producing no disability (Grade A). The orifice of the mitral valve may be reduced to half its normal size without the appearance of symptoms in a person who does not subject himself to unusual physical stress. Reduction of the cardiac output occurs, together with a limitation of the capacity to increase cardiac output on exercise. No rise of the pulmonary vascular pressures occurs.

Stage II. " Mitral orifice " 2 to 1·5 sq. cm. Grade B disability. Reduction in the size of the mitral orifice to this degree is associated with no symptoms in a sedentary life, but undue breathlessness may occur on much exertion. The cardiac index is reduced from 3·8 to 2·8 litres per sq. metre per minute, and a slight increase in pressure in the pulmonary circulation occurs, and this increases on exercise.

Stage III. " Mitral orifice " 1 sq. cm. Grade C disability. Further reduction in the size of the mitral orifice is associated with an inability to undertake moderate exertion. Little further decrease in cardiac output occurs, this being maintained by an increase in the left atrial pressure, with an equal increase in the pulmonary capillary pressure and pulmonary arterial pressure. An appreciable rise of pulmonary vascular pressures occurs on exercise.

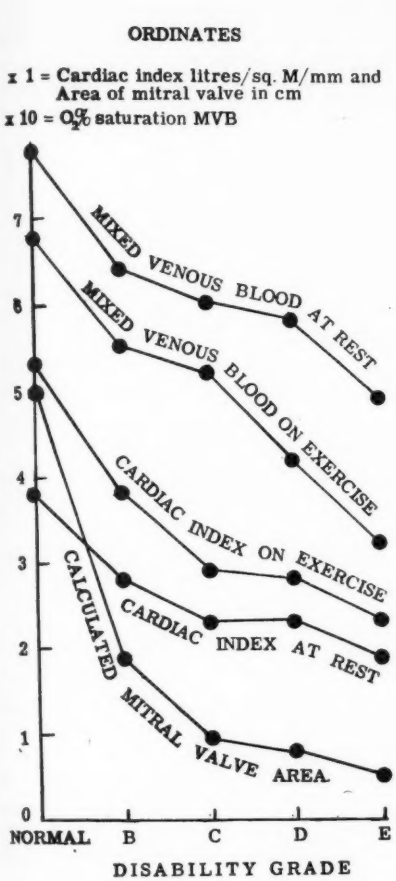

FIG. 1.—The normal value of "mitral valve area," cardiac index, and oxygen saturation of mixed venous blood, at rest and on exercise, compared with the mean of the same measurement at the four grades of disability.

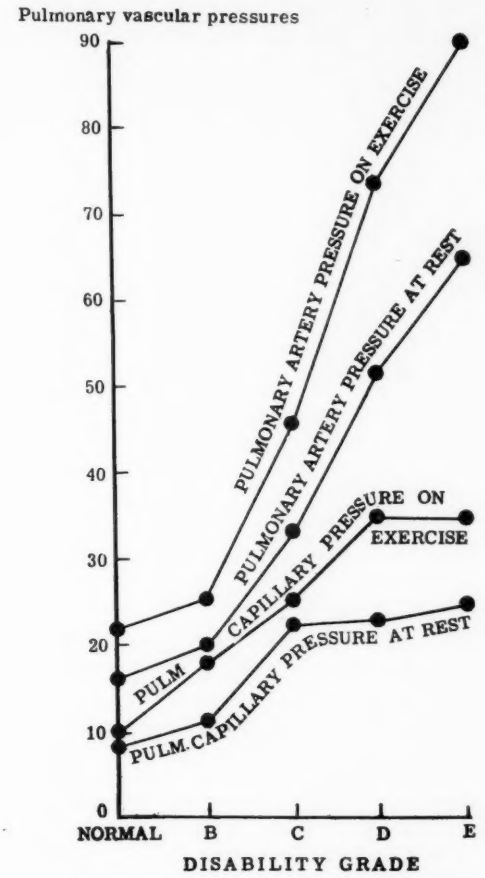

FIG. 2.—The normal value of the pulmonary capillary and pulmonary arterial pressures at rest and on exercise compared with the mean of the same measurements at the four grades of disability.

Stage IV. "*Mitral orifice*" *1 to 0·5 sq. cm. Grade D disability.* With more contraction of the mitral orifice a serious limitation of activity develops. The further reduction in cardiac output is slight, though impairment of the oxygen supply to the body is shown by the large fall in oxygen saturation of the mixed venous blood, especially during exercise. At this stage there is a slight further rise of the pulmonary capillary pressure and a greater rise in the pulmonary artery pressure both at rest and on exercise, indicating the development of pulmonary arteriolar resistance.

Stage V. "*Mitral orifice*" *0·5 sq. cm. or less. Grade E disability.* With such severe reduction of the orifice of the mitral valve the patient becomes confined to a life of chronic invalidism. The further reduction in cardiac output and rise of pulmonary capillary pressure is slight but the pulmonary artery pressure both at rest and on exercise is much increased. Further impairment of the oxygenation of the tissues is shown by a fall in the oxygen saturation of the mixed venous blood.

Effect of Atrial Fibrillation. This may supervene at any time during the progress of the disease and clinical experience shows that even if the heart rate is controlled, atrial fibrillation is likely to be associated with an increase in disability. Our observations show that the cardiac output is reduced when the atria fibrillate. There is a limitation of the ability to increase cardiac output on exercise, and this is associated with a reduction in stroke volume. If disability increases there is an associated rise in the pulmonary vascular pressures.

Effect of Myocarditis. The selection of patients for this study excluded those who had lesions of cardiac valves other than the mitral. As in the case of a similar group of patients described by Walsh *et al.* (1940) the attacks of rheumatic fever in most of our 81 patients had been mild and without frequent recurrences. We therefore believe that the incidence of myocarditis in them was not severe. Lesions resembling Aschoff bodies were seen in the endocardium in some of them, but the significance of these lesions is uncertain and reasons have been given for believing that they do not indicate active rheumatism (Enticknap, 1953). Atrial fibrillation, which occurred more commonly in the more seriously disabled patients, may be regarded as evidence of failure of the muscle of the atria, but it seems less likely to be due to myocarditis than to failure to contract against an increased atrial pressure. If atrial fibrillation should be due to active myocarditis it is difficult to explain why after operation patients with atrial fibrillation do as well, and perhaps better than, patients in sinus rhythm (Baker, Brock, and Campbell, 1955). The more seriously affected patients had pulmonary hypertension, and showed evidence of a hypertrophied and strongly acting right ventricle ; it seems unlikely, therefore, that the right ventricular muscle was weakened by rheumatic myocarditis. The cause of the disability remaining after a successful valvotomy is usually attributed to an incomplete opening of the valve but it may be due to myocardial disease. Even if this is so it must be admitted that myocarditis plays a minor role in the causation of symptoms in patients with uncomplicated mitral stenosis.

Breathlessness in Mitral Stenosis

The observations recorded here are relevant to the factors involved in the causation of exertional dyspnœa in patients who are not in congestive cardiac failure. Pulmonary congestion is regarded as an important factor in the breathlessness of heart failure and heart disease generally. This term implies engorgement of the alveolar capillaries and increased transudation from them when the filtration pressure exceeds the colloid osmotic pressure of the plasma proteins. The degree of pulmonary congestion is therefore to be related to the pulmonary capillary pressure and to the amount of fluid in the lungs, and if it plays an important role in the dyspnœa we should expect to observe a parallelism between the degree of breathlessness, the rise of pressure in the lung capillaries, and the evidence of increased fluid in the lungs.

With minor degrees of disability (Grades B and C) our findings correspond with the theory that pulmonary congestion plays a role in the causation of dyspnœa. But in the more severe grades of disability (Table I), pulmonary capillary pressure, both at rest and on exercise, shows little difference as the disability increases.

Though the pulmonary capillary pressure at rest is seldom higher than 30 mm. Hg it is recognized that the pulmonary arterial pressure may continue to increase in the pulmonary artery-pulmonary capillary pressure gradient (Gorlin, 1951). The increased pulmonary arteriolar resistance that this implies has been thought to protect the pulmonary capillaries from an undue increase in pressure. We find, as do other workers (Davies *et al.*, 1954) that, if such protection exists, it fails under the strain of very mild exercise (Tables I and IV), when the pulmonary capillary pressure rises sharply. After exercise we did not find clinical evidence of increased fluid in the lungs of more severely affected patients, though the pressure in the lung capillaries might have exceeded that of the colloid osmotic pressure of the plasma proteins. The patients quickly recovered and no basal râles were heard. These observations support Drinker's (1954) opinion that " heightened capillary pressure and stretching of the (alveolar) vessels does cause increase in the tissue fluid of the lungs, but this fluid enters the lymphatics rapidly and until they are filled with lymph and the restricted

entrance into the blood offered by the right lymphatic duct causes lymph stasis, obvious pulmonary œdema of conventional character is not seen. Something more than increased capillary pressure is necessary to cause œdema." We believe therefore that pulmonary congestion, as measured by the level of pulmonary capillary pressure, or clinical evidence of increased fluid in the lungs, does not play a primary role in the dyspnœa of patients with mitral stenosis, severely affected but not in cardiac failure.

The level of pulmonary capillary pressure at rest and on exercise is not closely related to the degree of dyspnœa on exertion, but the closer relation between pulmonary arterial pressure and dyspnœa requires further consideration. A possible mechanism by which pulmonary hypertension may contribute to the dyspnœa of mitral stenosis is suggested by the observations of Marshall *et al.* (1954). In respiratory studies on patients with mitral stenosis, not in cardiac failure, they found that the lungs are more rigid than normal, especially on exercise, so that an increased amount of work was necessary to ventilate them. Pulmonary vascular pressures were not measured, but they suggest the changes are due to pulmonary congestion ; our findings suggest that the changes are due to pulmonary arterial hypertension. That pulmonary hypertension is a factor in the causation of lung rigidity is also supported by observations we have made on patients with " primary pulmonary hypertension " in whom dyspnœa on exertion is associated with an increased pulmonary artery pressure, but with no marked increase in pulmonary capillary pressure or disease of the lung parenchyma.

The level of oxygen saturation of the mixed venous blood is a measure of the general level of oxygenation of the tissues, so that the value observed at the end of exercise is a measure of the oxygen debt incurred. In our studies on the level of oxygen saturation of mixed venous blood and the degree of disability we have in effect observed that the greater the ease with which exertional dyspnœa is evoked, the greater is the oxygen debt incurred in the performance of a standard exercise. This corresponds with the observations of Campbell and Sale (1927) and Stock and Kennedy (1953), who found that when a patient with mitral stenosis performs a standard exercise, more ventilation of the lungs takes place than in a normal subject, and the degree of disability can be related to the margin between ventilatory cost of exercise and the maximum ventilatory capacity of the patient. They suggest that the excess ventilation may be attributed to a large oxygen debt which arises because the blood flow to the tissues is inadequate to supply their need for oxygen.

Because the oxygen saturation of the mixed venous blood and the rise of the pulmonary artery pressure are both closely related to the degree of disability, we enquired whether the two changes were related to each other. This was found to be so, both at rest and on exercise (Fig. 3). This relationship may occur because the reduced oxygen tension of the mixed venous blood acts as a stimulus to pulmonary vasoconstriction, either by direct action on the vessels or through a reflex mechanism. Supporting the hypothesis of a causal relationship is the association of a reduction in venous oxygen tension and a rise in pulmonary artery pressure when a low concentration of oxygen is breathed by patients with mitral stenosis (McGregor *et al.*, 1953), and changes in the opposite direction when a high oxygen concentration is breathed. It is not proved, however, that the lowered oxygen saturation of the mixed venous blood in those observations is the stimulus that is responsible for the increase in pulmonary arterial pressure. The investigations of Duke and Killick (1952) indicate that the stimulus to elevation of the pulmonary artery pressure in animals breathing low oxygen concentration is most likely the oxygen tension in the alveoli. Therefore the occurrence of low venous oxygen saturation and high pulmonary artery pressure in a patient with severe mitral stenosis may be independent indications of the severity of his condition and show that a number of factors must be taken into account before we can fully understand the mechanism of dyspnœa in this condition.

Diagnostic Use of Cardiac Catheterization

Clinical Estimation of Pulmonary Arterial Pressure. We have shown that if patients are taken together in groups, the pulmonary artery pressure is closely related to the degree of disability. It is

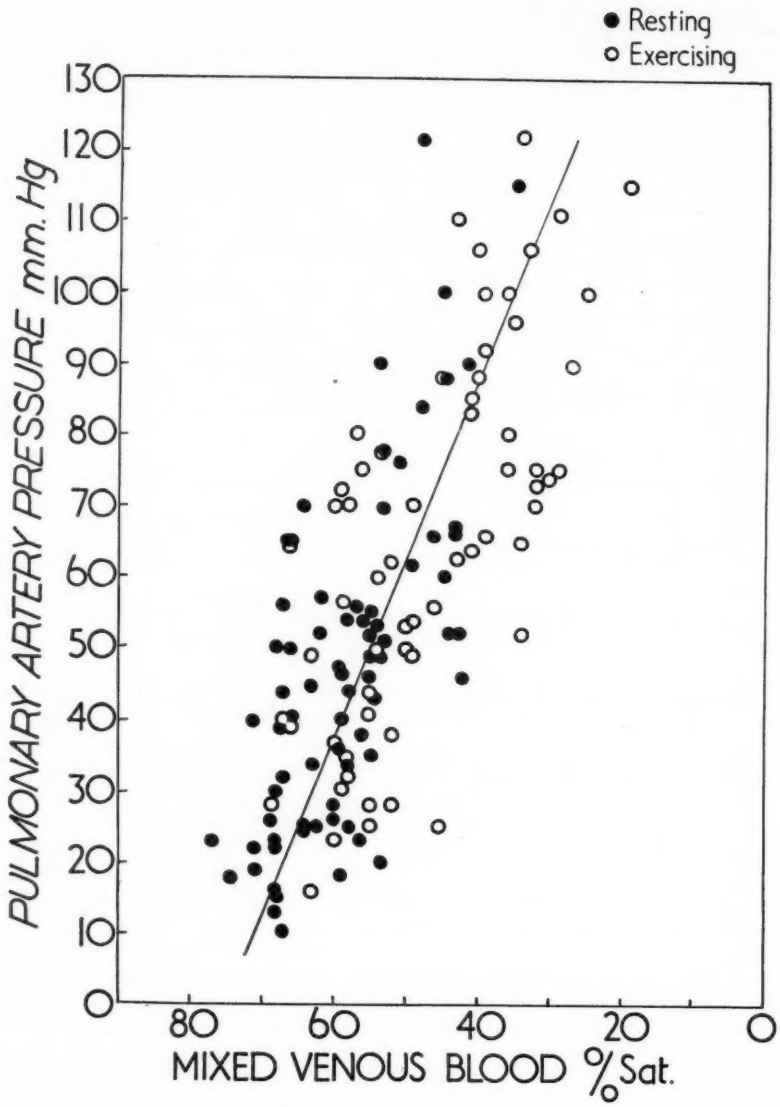

FIG. 3.—The relation of mean pulmonary artery pressure to oxygen saturation of the mixed venous blood in 81 cases of mitral stenosis.

therefore of interest to find whether the degree of pulmonary hypertension can be estimated from the physical signs and electrocardiographic and radiological features without the aid of cardiac catheterization. Our experience on this point is in substantial agreement with that of Whitaker (1954), who found that more frequently than by chance, a reasonable clinical estimate of the pulmonary artery pressure can be made. However, we find that our clinical assessment of

pulmonary artery pressure often shows a marked difference from the pulmonary artery pressure measured at cardiac catheterization, so that it cannot be relied on.

Investigation of Complicated Cases of Mitral Stenosis. Though cardiac catheterization was originally carried out in all patients being prepared for mitral valvotomy, it is now clear that most of the results did little more than support clinical judgment (Baker *et al.*, 1952). The investigation remains of considerable value in the diagnosis in such conditions as atrial septal defects, which may complicate mitral stenosis, but in general it is carried out only when the exact diagnosis is uncertain, or the significance of the signs of the complications not apparent.

The results obtained in patients with no cause for disability other than mitral stenosis serve as useful criteria for comparison with the findings in patients who have evidence of other causes of disability as well. Such patients have made up the majority of those referred to hospital for mitral valvotomy, the most frequently encountered complications being mitral incompetence, cardiac neurosis, aortic lesions, or chronic respiratory disease. In such patients it is necessary to decide whether the stenosis of the mitral valve is itself the cause of sufficient disability to justify the operation of mitral valvotomy. To help in this decision the results of the catheterization may be compared to the measurements (Tables I and III), that we have found to give an objective assessment of the degree of disability due to mitral stenosis. Unfortunately the findings at catheterization in patients in whom considerable mitral incompetence has been demonstrated at operation have not served to distinguish them with any reliability from patients with uncomplicated mitral stenosis. Moreover, experience with methods recently suggested as valuable in the differentiation of patients with mitral incompetence has not altered our opinion (Venner and Holling, 1953) that there is as yet no satisfactory method by which this can be done. In patients in whom cardiac neurosis was contributing considerably to their symptoms, we have found that the measurements made at catheterization indicated a degree of disability much less than that from which the patient was complaining.

Differences have also been found in patients in whom we have considered that aortic valve disease, of which there were definite signs, contributed considerably to their disability. In such patients a technically successful valvotomy has been followed by a disappointing clinical result, and the remaining disability has been ascribed to the disease of the aortic valves. Before operation these patients were found to have a lower pulmonary artery pressure and a higher degree of oxygen saturation of the mixed venous blood than the group of patients with the same degree of disability due to uncomplicated mitral stenosis.

In patients in whom it was considered that chronic respiratory disease contributed considerably to their symptoms and in whom the result of mitral valvotomy proved disappointing, we have also observed that the catheterization before operation showed a pattern of pulmonary pressures different from that shown by patients with uncomplicated mitral stenosis. In them the rise of pulmonary artery pressure was as high as in corresponding patients with uncomplicated mitral stenosis, but the pulmonary capillary pressure was lower. This corresponds with the findings of Yu *et al.* (1953) that chronic respiratory disease is associated with a high pulmonary artery pressure and a low pulmonary capillary pressure.

These comparisons are likely to be of assistance in the assessment of complicated cases of mitral stenosis before operation. Thus an opinion that either cardiac neurosis or aortic disease is contributing considerably to the disability of a patient with mitral stenosis is supported if the oxygen saturation of the mixed venous blood and the pulmonary artery and pulmonary capillary pressure are found to be less abnormal than corresponds to the degree of disability. An unexpectedly low pulmonary capillary pressure in a patient with mitral stenosis and chronic respiratory disease suggests that the respiratory disease is contributing considerably to the disability. In these patients a guarded prognosis of the results of operation is to be given.

Studies after Valvotomy: Evidence of Persistence of Changes in the Pulmonary Vessels. The observations made on patients after a successful mitral valvotomy have been examined for evidence of difference in the pulmonary circulation from unoperated patients suffering from the same mild

degree of disability. The problem was whether an alleviation of disability form Grade D or E before operation to Grade B after operation was accompanied by a restoration of the pulmonary circulation to that of unoperated patients with Grade B disability. To investigate this the findings in the 24 patients shown in Table IV who were improved from Grade D or E disability by operation have been compared with findings of unoperated patients of Grade B and C disability. In Table VI the relevant results have been abstracted from Tables I and IV. The patients who were of Grade B disability after operation were in some respects more abnormal than unoperated patients of Grade B disability, but always less abnormal than those of unoperated patients of Grade C disability.

TABLE VI

PULMONARY VASCULAR PRESSURES IN OPERATED AND UNOPERATED PATIENTS

Measurement	Mean pressure of group		
	7 Unoperated patients, Grade B disability	24 Operated patients, Grade B disability	18 Unoperated patients, Grade C disability
Pulmonary artery pressure, mm. Hg			
At rest	18·0	26·0	33·0
Exercising	26·0	44·4	46·0
Pulmonary capillary pressure, mm. Hg			
At rest	12·4	13·0	22·0
Exercising	20·0	23·3	25·0

The pulmonary artery pressure at rest in the patients after operation is higher than in patients of the same disability group who have not been operated on, the difference being highly significant, but the pulmonary artery pressure is significantly lower than that of unoperated patients of Grade C disability. On exercise the pulmonary artery pressure of operated patients corresponds to that of unoperated patients of Grade C disability. An obvious explanation of these findings is that some of the patients after operation had more disability than had been thought, the judgment of the patient and perhaps of his doctor having been biased by enthusiasm for the results of the operation. The obvious explanation, however, does not explain the pulmonary capillary pressures. These in the operated patients are the same as in unoperated patients of the same degree of disability, and the difference from that of patients of Grade C disability is highly significant. On exercise the pulmonary capillary pressure rises slightly more in the operated patients than in unoperated patients of Grade B disability. This shows that an increase in pulmonary artery-pulmonary capillary pressure gradient persists after operation and indicates that all the effects of severe mitral stenosis on the pulmonary circulation were not reversed at the time of the post-operative catheterization. This abnormality might be ascribed to the persistence of structural changes in the pulmonary vessels (Parker and Weiss, 1936) after operation.

SUMMARY AND CONCLUSIONS

From a large number of patients being considered for mitral valvotomy 81 were selected as examples of mitral stenosis with no evidence of mitral incompetence, chronic respiratory disease, cardiac neurosis, or disease of other heart valves. Twenty-five of the patients had atrial fibrillation. The disability from which each patient suffered was judged by enquiry into capacity for effort in everyday life. According to the degree of their disability the patients were divided into four groups.

Cardiac catheterization was used to make circulatory measurements on them at rest and during

a standard exercise. In 27 patients the circulatory measurements were repeated six months to four years after mitral valvotomy had been performed. The degree of disability of the patient during this interval was assessed.

The circulatory measurements of each group of patients were compared in order to determine which measurements most clearly discriminated between groups of patients of different degrees of disability, with the following results. The pulmonary artery pressure measurement affords a good means of discriminating between all groups of patients. The oxygen saturation of the mixed venous blood discriminates clearly between the three more severe grades of disability. Though cardiac output shows some reduction with increasing disability the relationship is not close enough to afford a satisfactory means of discrimination. " Pulmonary arterial resistance," pulmonary capillary pressure, left atrial pressure (at operation), and the calculated " mitral valve area " discriminate between some groups of disability.

The relationship between disability and circulatory measurements in patients in sinus rhythm and with controlled atrial fibrillation was investigated. With the same degree of disability the cardiac output at rest was lower when there was atrial fibrillation, and the increase on exercise was less; the differences, however, were not significant. With the same degree of disability, there was no significant difference between the two categories of patients in the pulmonary vascular pressures or in the oxygen saturation of the mixed venous blood.

The results obtained indicate the circulatory changes that are associated with increasing disability in the average case of mitral stenosis. With the first appearance of symptoms the mitral orifice is calculated to be reduced to half its normal area and the cardiac output reduced by a quarter: there is little rise of the pulmonary vascular pressure. With further increase in disability the greatest changes occur in the pulmonary arterial pressure and the oxygen saturation of the mixed venous blood, the least in the cardiac output.

A rise of the pulmonary arterial pressure may be a more important cause of severe dyspnœa than a rise of pulmonary capillary pressure, because the height of the latter is similar in the three groups of more disabled patients, while the former shows a significant difference from group to group. The increased tendency to dyspnœa could be explained by the lungs being made more rigid by the increase in pressure within their arterial network. The association between disability and oxygen saturation of the mixed venous blood has been found to be closer than that between disability and cardiac output. The reason for this is that the reduction of cardiac output is but one of the factors affecting the carriage of oxygen to the tissues, other factors being a reduced arterial oxygen blood saturation and a reduction in oxygen carrying capacity of the blood in severe mitral stenosis. The measurement of the oxygen saturation of the mixed venous blood provides a comprehensive measure of the effect of these factors.

The degree of depression of the oxygen saturation of the mixed venous blood and of elevation of the pulmonary arterial pressure are related to each other. No cause for this relationship is suggested except that the two changes are independent indications of the severity of the patient's condition.

When the findings at cardiac catheterization in patients with mitral stenosis complicated by other conditions are compared with the findings in the 81 patients here described, differences can be shown that may be of assistance in deciding to what degree the disability of a complicated case is to be attributed to the existing mitral stenosis. No satisfactory method of distinguishing the effects of mitral regurgitation has been found. When mitral stenosis is complicated by cardiac neurosis the measurements indicate a degree of disability less than that from which the patient is complaining. The patients in whom aortic valve disease contributes considerably to their disability show a lower pulmonary artery pressure and a higher degree of oxygen saturation of the mixed venous blood than the group of patients with the same degree of disability due to uncomplicated mitral stenosis. The association of mitral stenosis and chronic respiratory disease results in the pulmonary artery pressure being as high as in uncomplicated cases of mitral stenosis of the same degree of disability, but the pulmonary capillary pressure is lower.

Evidence of the persistence of pulmonary vascular changes in patients whose severe mitral stenosis has been relieved by mitral valvotomy has been found. This is suggested by the finding of a higher pulmonary artery-pulmonary capillary pressure gradient in patients after operation than in patients with the same degree of disability who have not been operated on.

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LORD HORDER

Thomas Jeeves Horder was born on January 7, 1871 at Shaftesbury in Dorset, and died at Ashford Chase, near Petersfield on August 13, 1955, aged 84. The period of his medical life coincided with the era in which the general physician reached his fullest development: Horder was probably the most clinically acute member of that now rare group. The great flood of knowledge of the last generation has made it impossible for any man to be efficient in more than one aspect of medicine.

Horder was educated at Swindon High School and at St. Bartholomew's Hospital, where he won the entrance scholarship in 1891. He obtained the London M.B. with first class honours in 1897 and the M.R.C.P. and the London M.D. in 1899. He became House Physician to Samuel Gee and when Gee's *Clinical Lectures* were republished in 1906 he added many of Gee's aphorisms. Soon after this he started in consulting practice and was on the honorary staff of the Royal Northern Hospital, but it was not till 1912 that he was appointed to the staff of St. Bartholomew's. He became Senior Physician in 1933 and retired under the age limit in 1936.

He was knighted in 1918, made a baronet in 1923 and, ten years later, was raised to the peerage as Lord Horder of Ashford. He became G.C.V.O. in 1938.

He married in 1902, Geraldine, daughter of Arthur Doggett, and his wife died a year before him: they had one son and two daughters.

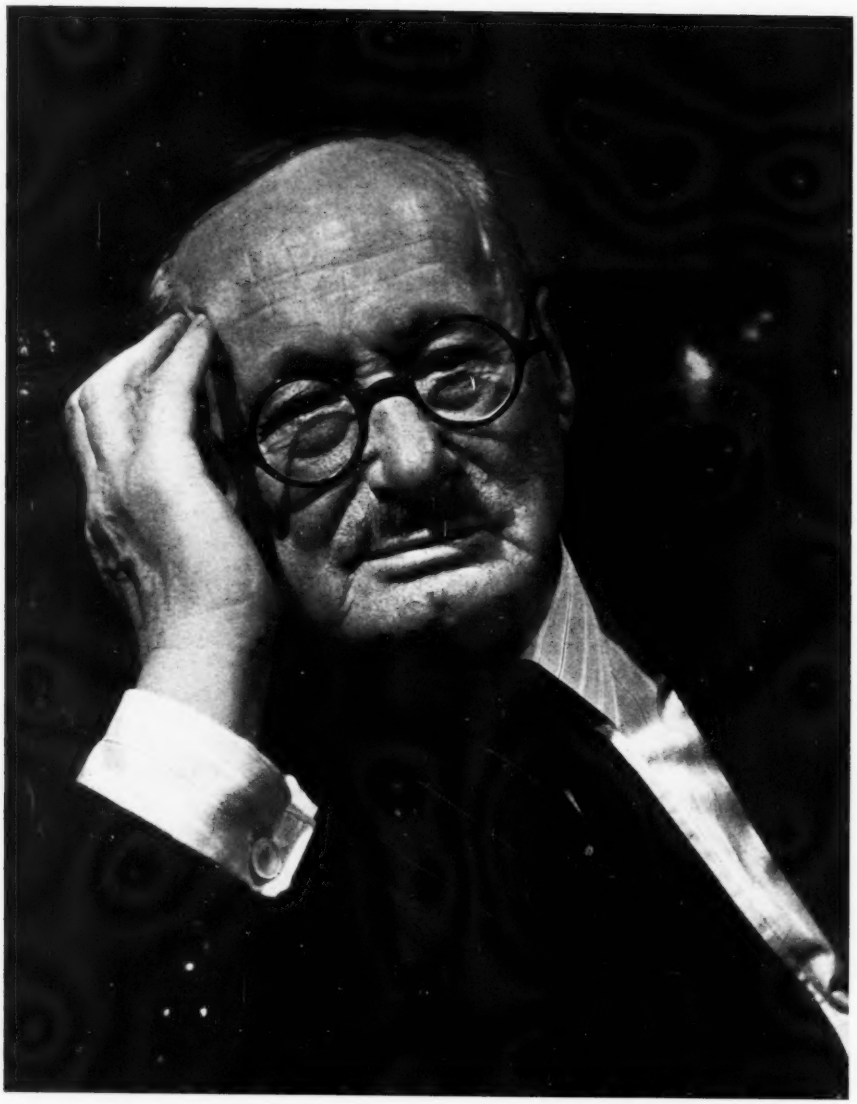
Horder's wide view of his profession never allowed him to become a cardiologist in the modern sense, and for this reason the passage of years slowly separated him from the cardiological world. He was, however, an original member of the Cardiac Club and attended the meetings regularly until he became an Extra-Ordinary member after his retirement. In 1922 he opened a discussion on infective endocarditis. This subject was the one in which he made his chief scientific contribution to cardiology. His work on the bacteriology of the disease, in which he was closely associated with Sir Frederick Andrews, was original and that of a pioneer. He was also interested in the ætiology of acute rheumatism, and by blood culture studies concluded that in this condition there was no streptococcal bacteriæmia.

In spite of his general approach his opinion in heart cases was sought to the end of his life. The reason was that his clinical judgement and his shrewd common sense so often revealed an essential fact hitherto hidden in a thicket of pseudo-scientific minutiæ. On one such occasion, in consultation with a cardiologist, after inspecting pathological reports and numerous cardiograms, he insisted on examining the lung bases although the patient was said to be too ill to move: a large posterior pleural effusion was discovered and removed, to the patient's lasting benefit.

The gift for collecting the facts that are reliable and have a direct bearing on diagnosis and prognosis, and of discarding those that are misleading or of less weight constitutes the sense of values inherent in a good clinician. Horder had this quality in its most valuable form. He was undisturbed by environment, occasion, or by previously expressed opinions. "If I am told a patient is suffering from this or that disease I do my best to disprove the statement," he once said to the writer. "If the diagnosis is wrong I have the best chance of finding this out. If it is right and I am forced to agree, the corroboration becomes valuable." With these qualities it is natural that he had a large consulting practice. He was medical adviser to many famous people, including three Kings and three Prime Ministers.

His was the scientific approach to medicine, to human activities, and to life as a whole. In other words he wished in all things for truth, and scorned falsity in all its forms. The opinion of the humblest house physician was considered by him strictly on its merits; the bombast of a pompous politician was treated in the same way.

He had an unusually wide range of interests and thought all these important because of his belief that medicine was one of the social sciences. Among these were the National Birth Control Association, the Eugenics Society, the National Smoke Abatement Society, and the Empire Rheumatism Council, and in many of these he took a leading part. He did not see why human beings should not be helped to become sensible in such matters as eugenics, cremation, birth-control, and noise abatement. In such matters he was not content to issue polemics: he entered the combatant lists, and fought hard himself.



[*Reproduced by permission of Douglas Glass*

LORD HORDER

It was this quality of fighting for what he felt was right that caused him to found the Fellowship for Freedom in Medicine. He knew that medicine was basically an affair of two individuals—the doctor and the patient—and he saw plainly the dangers to medical practice threatened by so many aspects of a State Medical Service: the entry of the State, as a third person, into the relationship was a potential menace. He was never against a scheme in which finance, on a contributory basis, could be organized by the State, but he felt strongly that the medical side of any scheme should be organized and run by the medical profession.

He was all his life an individualist, and therefore in his later years became unfashionable, for it is now often forgotten that without the scientific advances of individualists this age of the common man could not exist. As an individual, although of relatively humble origin, he fought his way onto the staff of St. Bartholomew's, in the face of conservative medical and social orthodoxy at its most formidable. As an individual he made his way as a consulting physician, utilizing, as an aid to his native genius, the new weapons of clinical pathology which his seniors lacked. In his early days he did his own blood counts, sputum and urine examinations, and bacteriology. This approach to diagnosis took him quickly to the front rank of consulting clinical practice.

In the 1939–45 war he performed valuable services as chairman of a government committee that advised about the health measures needed for the large air raid shelters, such as the London tubes, and the absence of serious epidemics must owe something to his wisdom. He was also one of the advisers to Lord Woolton at the Ministry of Food. His wide interest in the social aspect of medicine is well shown in his volume of reminiscences, *Fifty Years of Medicine*, that was published in 1952.

It was not professional ability alone that made him a great man, for he had all the personal attributes of a fine character. He was honest, courageous, lovable, intensely interested in his fellow men, and generously self-sacrificing. In the 1918 influenza epidemic, when he was excessively busy, he came to the Evelina Hospital on several successive nights to visit the writer, previously his house-physician, who was seriously ill with the infection. "Bourne and I are friends" was his reply to someone commenting on his kindness. This action was typical of him.

His brisk actions and the penetrating timbre of his slightly harsh voice were vehicles of his wonderfully vivacious and active mind. His comments, in the face of pomposity or self-important stupidity, could be cutting. His outspokenness was symptomatic of his desire for truth for its own sake. His vitality shone brightly to the end of his life. Every weekend he drove himself down to Ashford Chase, where he worked in the unique and lovely garden he had made. He was greatly blessed in that his sparkling mind, his greatest gift, retained its lustre to his last hours. His was a great life.

GEOFFREY BOURNE

CASE REPORTS

SADDLE EMBOLUS OF THE AORTIC BIFURCATION TREATED BY EMBOLECTOMY

BY

A. K. BASU AND A. DAS

From the Nilratan Sircar Medical College, Calcutta

Sudden occlusion of the aorta usually occurs at its bifurcation and is due to lodgement of an embolus. A blood clot sufficiently large to straddle the aorta usually comes from the atrium in a case of mitral stenosis. The importance of this ætiological factor was stressed by Banowitch and Ira (1928). Hermann *et al.* (1943) discussed the clinical manifestations and treatment of this condition. By 1950, 200 cases of saddle embolus of the aorta had been recorded; 75 per cent of these died. Of these cases, eight were reported to have been cured by conservative management and there were four spontaneous recoveries. Up to this time, Albright and Leonard (1950) recorded 26 cures after successful embolectomy and Ewing (1950) also recorded 13 more survivals, including two of his own cases.

Case Report

A woman, aged 27, with mitral stenosis, was admitted into hospital for assessment of suitability for valvotomy. She had normal sinus rhythm. Her blood pressure was 118/70. There was a systolic murmur over the left second and third intercostal spaces lateral to the sternum which led to the suspicion of atrial septal defect. Electrocardiographic and radiological findings were consistent with the diagnosis of mitral stenosis. At cardiac catheterization the pressure in the right atrium was within normal limits but the right ventricular pressure was raised (390 mm. of saline). The catheter could not be introduced through a septal defect after repeated trials, and failed also to enter the pulmonary artery.

Two days later, while trying to get out of bed, she felt a sudden "shock-like" sensation in both lower limbs followed by intense pain in the legs and feet. Within half an hour, the pain of the right leg and foot became agonizing, while on the left side, the pain abated and there was only numbness.

Clinical findings. When examined about an hour after the onset she was restless and in great agony. The temperature was normal. There was slight sweating of the forehead and face. Pulse was 110 a minute. Blood pressure measured 146/90. There was no abdominal tenderness.

The following signs were found on examination of the inferior extremities. Both legs were cold, the right more than the left. All arterial pulsation below Poupart's ligament was absent in both limbs. On the right side, there was loss of power of all the muscles of the leg and she could not move her ankle or toes. There was only slight loss of power of the muscles of the thigh and flexion and extension of the knee could be carried out. There was complete loss of sensation up to the knee on the right side. On the left side, the loss of power and sensation below the knee was very slight. The diagnosis of saddle embolus at the aortic bifurcation with complete blockage of the right common iliac and partial blockage of the left was made. An operation was decided upon. While preparations for this were being made, slight cyanosis developed in the toes and foot of the right side.

Operative procedure. The operation was started at about five and a half hours after the occurrence of embolism. The abdomen was opened by a 15-cm. right paramedian incision. With the patient tilted in 30 degree Trendelenburg position, the bifurcation of the aorta and the two common iliacs were exposed by incising the posterior parietal peritoneum. There was absence of pulsation in both common iliacs, as also at the aortic bifurcation. A fair sized bulge could be seen at this site, particularly at the commencement of the right common iliac artery and the abrupt contrast in the size of the vessel between the bulged portion and the narrow portion below it was striking.

Broad cotton tapes were passed around the abdominal aorta below the inferior mesenteric artery and around the right common iliac distal to the thrombus. A 1·25-cm. incision was made on the anterior surface of the right common iliac artery directly over the swollen portion and just distal to the aortic bifurcation. As the lips of this incision separated, the dark thrombus was clearly discernible.

A No. 6 catheter lubricated and connected to a suction tap, was manœuvred beside the thrombus between it and the vessel wall but dislodgement by this method appeared improbable and the attempt was abandoned. The lower tape had been tightened during this procedure. The trunk of the abdominal aorta was next gently squeezed by fingers just proximal to the thrombus and as this was done, the thrombus could be seen protruding in the opening between the lips of the incision and suddenly came out with a great deal of force followed by a huge gush of blood. As the tape around the abdominal aorta was tightened, the flow of blood was quickly controlled. The walls and the lumen of the vessel appeared healthy on inspection. The opening in the common iliac was closed by one layer of eversion continuous mattress suture using 5/0 Deknatel silk on a half-curved atraumatic needle. The distal tape was loosened first and after about 3 minutes of local pressure over the suture line, the aortic tape was also loosened. There was no significant leak and no additional sutures were required. Vigorous pulsation came back immediately to both external iliac and femoral arteries. The posterior parietal peritoneum was repaired and the abdomen closed.

About half way through the operation the patient developed auricular fibrillation and the ventricular rate went up to 160 a minute. I.V. digoxin was given, and this controlled the ventricular rate to some extent so that at the end of the operation, the patient had a heart rate of 120 a minute still with fibrillation.

Six hours after the operation, the heart rate had fallen to 110; fibrillation was still present but there was spontaneous reversion to sinus rhythm a few hours later. Pulsation was present at all levels of the left leg, and at the femoral and popliteal levels on the right side, but was absent in the right posterior tibial and right dorsalis pedis at the ankle. However, both the limbs were warm and there was no doubt about the restoration of the essential circulation in the right foot and leg. The patient was able to move her legs but there was still partial loss of sensation and motor power over the right foot and leg.

Twenty-four hours later, there was pain over the right calf which was somewhat swollen, œdematous and indurated. It was quite tender to pressure. Diagnosis of deep venous thrombosis at this level was made. Femoral and popliteal pulsations were present but pulsations in the posterior tibial and dorsalis pedis were still absent. The essential circulation in the right foot and leg was still considered adequate. There was partial loss of sensation and motor power in the right leg and foot. The limb was surrounded in an ice pack and I.V. heparin therapy was started, the calf œdema and induration gradually disappeared over a course of about three weeks.

At the time of reporting, the sensory loss has disappeared completely on both sides but there is residual weakness of the dorsiflexors and evertor muscles of the right foot. Pulsations have also returned in the right posterior tibial and dorsalis pedis arteries.

Discussion

As the embolism occurred within 48 hours of cardiac catheterization, it may be suspected that the procedure was in some way responsible for the complication. However, as the left atrium was not entered, it is highly improbable that there was any causal relationship.

There is divergence of opinion as to the best method of exposure of the site of lodgement of the embolus. Murray (1943), who reported five personal cases, preferred the extraperitoneal approach. The intraperitoneal exposure, however, is direct, easy, and allows of better control of the vessels. Some surgeons have preferred incising the aorta directly instead of the common iliac artery and Ewing (1950), after his experience of two cases, was of this opinion. In the present case, the incision directly over the bulge in the common iliac appeared very satisfactory and the clot discharged itself *en masse* with slight proximal squeeze.

It may be noted that pulsation did not return in the dorsalis pedis and posterior tibial arteries on the right side for about three weeks after the operation. This may have been due to dislodgement of a fragment from the main embolus at the time of operation and its arrest at the lower level. This explanation appears to be unlikely as the large sized thrombus was discharged *en masse* and was found to be unbroken and intact (Fig. 1). Also, the tape around the common iliac had been tightened during manipulation, reducing still further the chances of distal embolism.

Another explanation for this delay could be vascular spasm at distal levels of the limb due to

prolonged ischæmia of about five-and-a-half hours duration between the onset of the embolism and its relief by operation. This hypothesis appears most likely in the present case and it might also have contributed to the thrombotic complication in the deep veins of the calf, which developed 24 hours after the operation and gradually subsided. Possibly, a simultaneous lumbar sympathectomy at the time of embolectomy could have obviated this condition and it appears to us that when the interval between embolism and operation approaches six hours or more, sympathectomy should be seriously considered. Albright and Leonard (1950) are of similar opinion. In the present case, the auricular fibrillation which occurred during the operation made us decide against further prolongation of the operation.

FIG. 1.—Photograph of aortic embolus (contracted, × 3/4, after preservation in formol saline).

Another interesting feature was the remarkable localization of loss of power and sensation below the knee. In contrast, the upper half of the limbs were only slightly affected. It is probable that the difference in the arterial supply of the femoral and sciatic nerves may have been responsible for this disparity since the upper roots of the lumbar plexus derive their blood supply from above the aortic bifurcation, whereas the arterial supply of the sciatic nerve comes mostly from the internal iliac artery.

Summary

A case of mitral stenosis awaiting valvotomy suddenly developed a saddle embolus at the aortic bifurcation. This was treated by embolectomy. Comments are made on certain interesting features before, during, and after operation.

We are thankful to Dr. A. K. Dutt Gupta, Principal, Nilratan Sircar Medical College, for permission to publish this case. Our thanks are also due to Dr. S. Chatterjee for taking the responsibility of administering the anæsthetic.

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A CASE OF EBSTEIN'S ANOMALY SURVIVING TO THE AGE OF 79

BY

J. C. L. ADAMS AND REGINALD HUDSON

From the West Middlesex Hospital, Isleworth, and the National Heart Hospital

In 1866 Ebstein described an uncommon congenital abnormality in which the tricuspid valve was situated below its normal site, thus reducing the size of the functioning right ventricle. Since then, many examples have been recorded, some with " patent foramen ovale," and others without it; the most recent was by Kerwin (1955), who described a case diagnosed during life. In Abbott's series of 16 examples of Ebstein's anomaly, the oldest survived to 56 years. The present case is believed to be the longest survival yet recorded, and was a woman of 79 who succumbed to suppurative cholangitis.

Case Report

A woman, aged 79, was admitted to the West Middlesex Hospital in October, 1954, with a diagnosis of obstructive jaundice. She had been well until two days before admission, and had never complained of shortness of breath or of swelling of the ankles, though a relative said that the patient did go blue on undue effort, particularly in cold weather.

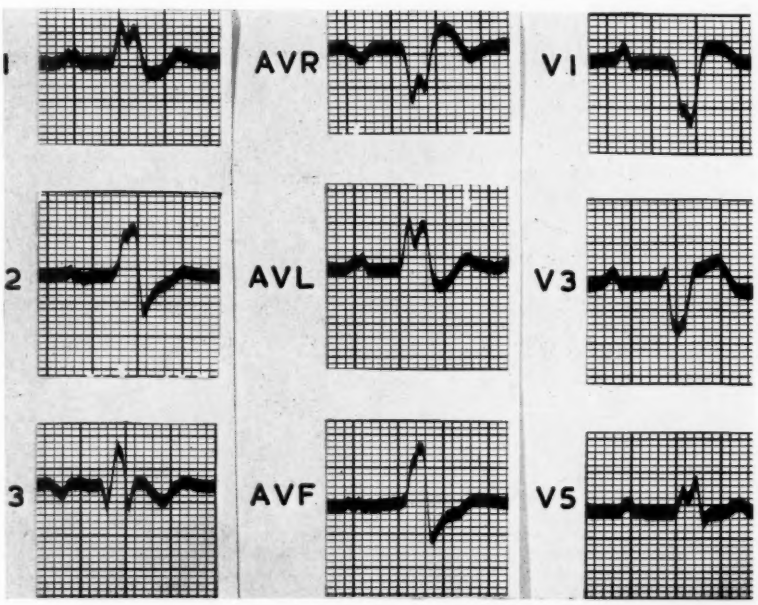

FIG. 1.—Electrocardiogram, showing long P–R interval and left bundle-branch block (QRS 0·16 sec.)

On admission, the patient who was rather obese, was jaundiced and extremely ill, with a temperature of 101·4° F., and a regular pulse of 120 a minute. There was no œdema. The jugular venous pressure was not raised and the apex beat was impalpable. The heart sounds were normal and no bruits were heard. The blood pressure was 135/80. The urine contained bile salts and bile pigments. The electrocardiogram (Fig. 1) showed auriculo-ventricular block and left bundle-branch block. The serum bilirubin was 11·6 mg./100 ml., alkaline phosphatase 46·7 King-Armstrong units, and the hæmoglobin 18·9 g./100 ml. Circulation-time tests were unsuccessful. On the day following admission, the patient showed slight cyanosis of the lips, ears, and hands, and death occurred the same day.

Necropsy. This was performed by Dr. A. C. Counsell of the West Middlesex Hospital, who reported that the *gall bladder* was small and thick-walled, with an obstruction by a calculus 2×1×1 in. The *liver* showed nutmeg pattern, and the larger bile ducts contained thick turbid bile. Histology of the liver showed a well marked chronic cholango-hepatitis, with irregular enlargement and chronic inflammatory cell infiltration of the portal tracts, and bile thrombi in the centrilobular canaliculi.

Dr. Counsell noted the right heart and tricuspid valve were grossly abnormal and kindly allowed one of us (R.H.) to make a further study of the heart. Fig. 2 is a view of the right heart of the specimen as received. Its weight was 431 g.

The true *right atrium* (R.A.) was moderately dilated, with an ostium secundum atrial septal defect (O.S.) about 1·7 cm. across, bridged by a filament of septum primum. The junction between true atrium and

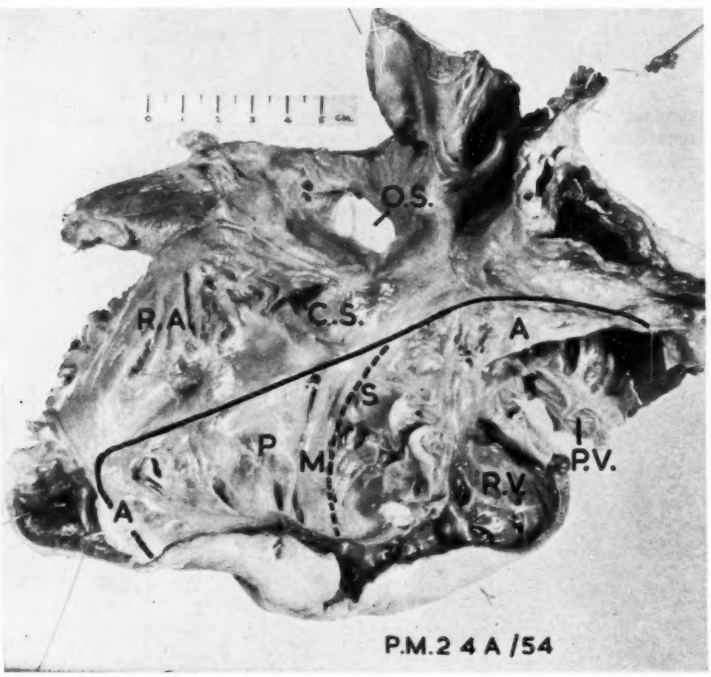

FIG. 2.—Ebstein's anomaly—right heart. R.A., right atrium; O.S., ostium secundum atrial septal defect; C.S., coronary sinus opening; AA, P, and S, anterior, posterior, and septal cusps of tricuspid value. Ventricular wall membranous at P. M, muscle band; R.V., functioning right ventricle; P.V., pulmonary valve. Continuous line indicates the atrio-ventricular junction and the normal origin of the tricuspid valve leaflets. Dotted line indicates the actual position of the valve ring, which joins the normal ring where the anterior cusp arises.

ventricle was quite distinct (continuous line). The functioning right atrium included approximately the upper four-fifths of the ventricular chamber.

The *tricuspid valve* was quite abnormal and difficult to interpret. The anterior cusp which was cut across (AA) was thickened and arose from the normal valve ring (continuous line). The free edge was thickened but the cusp was mobile. The chordæ tendineæ and papillary muscles were rudimentary. The posterior cusp (P) appeared to be functionless and stuck down on to the ventricular wall. Its lower fringe was attached to a broad muscle band (M) by tiny, rudimentary chordæ tendineæ (not visible in the photograph). The wall of the ventricle underlying the cusp at P was translucent and almost devoid of muscle over an area about 4 cm. across. Just below the muscle band (M) were a few calcified nodules. The septal cusp (S) was also largely fused to the ventricular wall, and its upper limit appeared to be in the position marked by the dotted line. The lower fringe of the septal cusp was oddly sacculated and showed a few rudimentary chordæ tendineæ and papillary muscles. The tricuspid valve orifice thus appeared to be functionally bicuspid, guarded in front by the thick lower edge of the anterior cusp and behind by the sacculated remnants of the septal cusp.

The funtioning right ventricle (R.V.) was reduced to about one-fifth of the true ventricle, and its wall was thinned to 2 mm. The upper four-fifths of the true right ventricle was functioning as right atrium, and was mostly lined by adherent tricuspid valve cusps. The pulmonary valve (P.V.) ring was reduced to 6 cm. The right anterior cusp was larger than the other two. The pulmonary trunk was correspondingly hypoplastic. The left atrium was moderately dilated and the left ventricle a little dilated and its wall 1·3 cm. thick. The mitral valve ring measured 9·0 cm. and the cusps showed slight nodular marginal thickening. The chordæ tendineæ were normal. The aortic valve ring measured 7·5 cm. and the cusps showed minimal thickening. There was mild atheroma of the aorta around the aortic valve. The coronary arteries were normally placed and showed only mild atheroma. The ductus arteriosus was closed (Dr. Counsell).

Discussion

Reference to embryological development suggests how the condition might arise. The atrio-ventricular valves arise by proliferation of subendocardial tissue of the atrio-ventricular canal and of the fused endocardial cushions (which divide the canal into tricuspid and mitral orifices) (Fig. 3A). These proliferations become excavated on their ventricular surfaces (X) but remain connected to the ventricular wall by muscular strands which differentiate into papillary muscles and chordæ tendineæ. Irregular or partial failure of this excavation process would result in the affected part of the valve outgrowth seeming to be adherent to the ventricular wall, the free

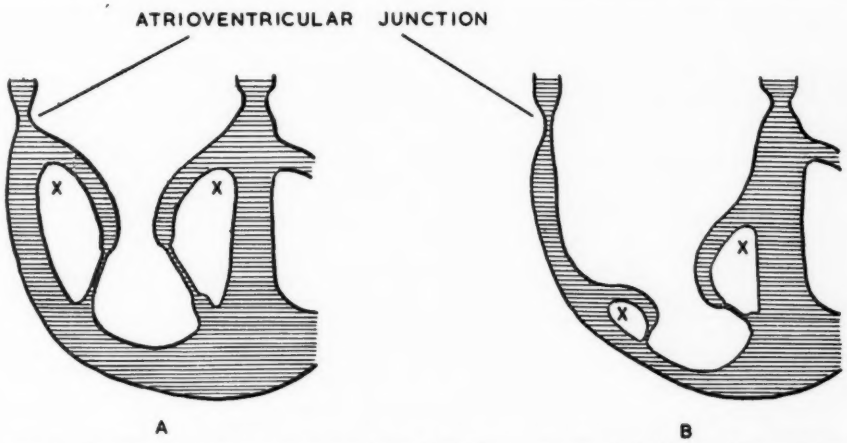

FIG. 3.—Diagram to show how the excavation at X which occurs normally in (A), on the ventricular aspect of the proliferations which form the atrio-ventricular valves might be partially arrested in Ebstein's anomaly (B) so the valve cusps appear to arise well below the atrio-ventricular junction, and the chordæ tendineæ appear to be short

portion of the cusp being much reduced so that the valve ring appears to be below the atrioventricular junction (Fig. 3B).

This case illustrates well that gross abnormality of the tricuspid valve and right ventricle in Ebstein's anomaly does not necessarily lead to a defective circulation, and it is quite compatible with a long healthy life.

Summary

The finding of Ebstein's anomaly is reported in a woman who survived to the age of 79 with no symptoms referable to the cardiovascular system, and who died from an unrelated disease.

We would like to express our thanks to Dr. N. F. Coghill for permission to publish this case and to Dr. A. C. Counsell for carrying out the necropsy.

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CONGENITAL TRICUSPID INCOMPETENCE

BY

D. W. BARRITT AND H. URICH

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Congenital tricuspid incompetence is rare and the following case is, therefore, worthy of mention.

Case Report

A boy of four years was first referred to the school cardiac clinic on account of a murmur heard at a routine examination. He had had pneumonia a year previously. He had not yet begun to talk. On examination at that time there was no cyanosis. A loud systolic murmur, accompanied by a thrill, was heard at the apex. An orthodiagram of the heart shadow showed prominence of the right auricle in the P.A. view. The cardiogram showed sinus rhythm with right bundle-branch block. He was seen at yearly intervals and at the age of 10 cardiac enlargement was detected clinically. The thrill and murmur were unchanged. The cardiogram again showed sinus rhythm and right bundle-branch

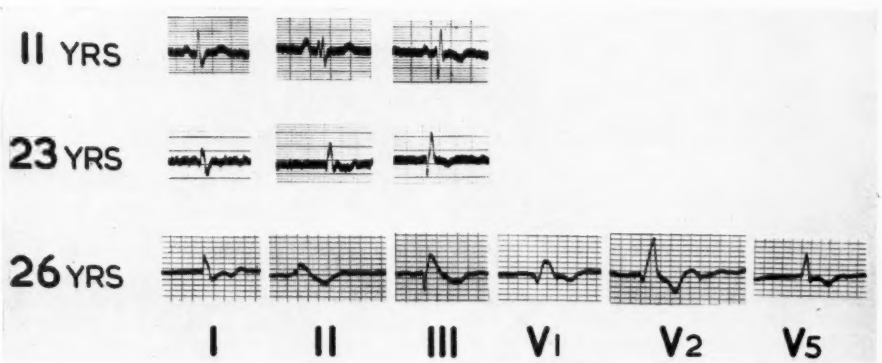

FIG. 1.—Serial electrocardiograms in congenital tricuspid incompetence.

block. The chest X-ray showed generalized cardiac enlargement and diminished pulmonary artery shadows. He left school at 14 years and was then noticed to have blue lips and hands, but no finger clubbing. Sinus rhythm was still present. When next seen at 22 years he was working as a milk roundsman. His blueness was more marked but there was still no clubbing. The heart was now much enlarged (Fig. 2). The systolic thrill and murmur were unchanged. For the first time a very striking systolic pulsation was noted in the neck veins. There was also marked systolic pulsation of an enlarged liver. Auricular fibrillation was now established. In the next five years the heart progressively increased in size. The neck veins became more prominent, and a large mass of tortuous veins extended from the neck over the clavicles. Systolic pulsation was always most striking and a similar pulsation could be felt over a grossly enlarged liver. The systolic thrill and murmur gradually diminished and were finally lost. He remained cyanosed, but showed no finger clubbing. At the age of 25 his hæmoglobin was 120 per cent and arterial oxygen saturation 90 per cent.

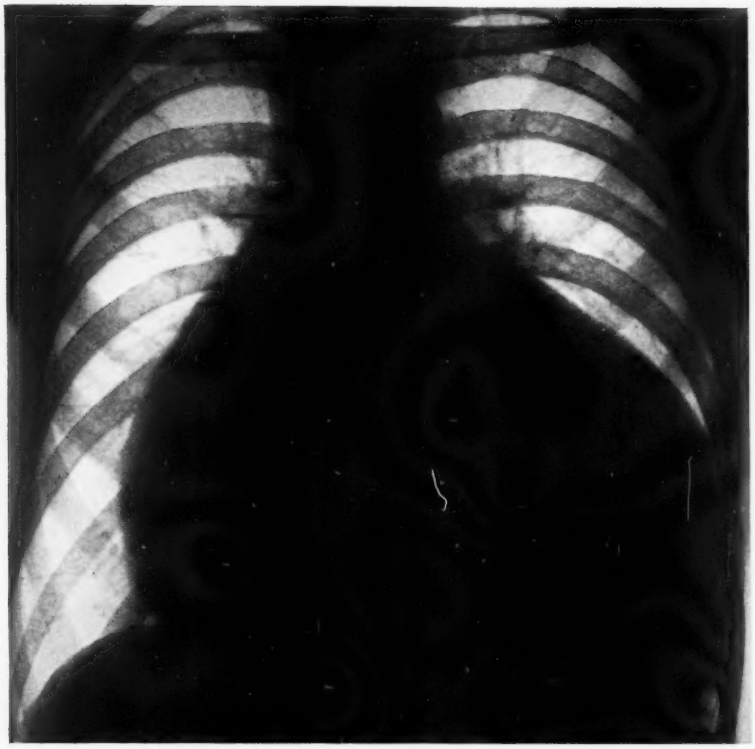

FIG. 2.—The chest radiogram at 24 years of age, showing great enlargement of the heart and small pulmonary artery shadows.

In the last two years of his life he was admitted several times to hospital with acute respiratory infections. Œdema of the ankles and ascites became gross. He was progressively more disabled, and died at the age of 28 of congestive heart failure.

Post-Mortem Findings. The subject was a thin young man in severe congestive heart failure with œdema, gross ascites, small bilateral pleural effusions and chronic venous congestion of all organs. *The pericardial cavity* contained about 100 ml. of bloodstained fluid. Both visceral and parietal surfaces were covered with shaggy fibrinous deposit. There were no adhesions. *The heart* weighed 700 g. *The right atrium* was enormously dilated and hypertrophied and received grossly dilated superior and inferior venæ cavæ and coronary sinus. There was mural thrombus in the auricular appendage. The right A-V orifice was enormously dilated (circumference 26 cm.). *The tricuspid valve* consisted of two cusps, anterior and fused postero-septal, both attached to the A-V wall by short and slender endocardial cords which immobilized the cusps (Fig. 3). The chordæ tendineæ were short and slender and were attached to two papillary muscles of which the posterior was small and rudimentary. *The right ventricle* was grossly dilated and hypertrophied (thickness 1·1 cm.), the enlargement involving predominantly the inflow tract. The pulmonary orifice and valve were normal. The left atrium was normal apart from slight endocardial thickening. The left A-V orifice was normal (circumference 9 cm.). *The mitral valve* showed some thickening and nodularity of the cusps, but no shortening or fusion. There were several flat yellowish vegetations distributed irregularly along the cusp margins and spreading on to slightly thickened chordæ tendineæ. *The left ventricle* was normal (thickness 1·3 cm.). The aortic valve showed a few flat yellowish vegetations near the cusp margins, but was otherwise normal. The interauricular and interventricular septa and the ductus

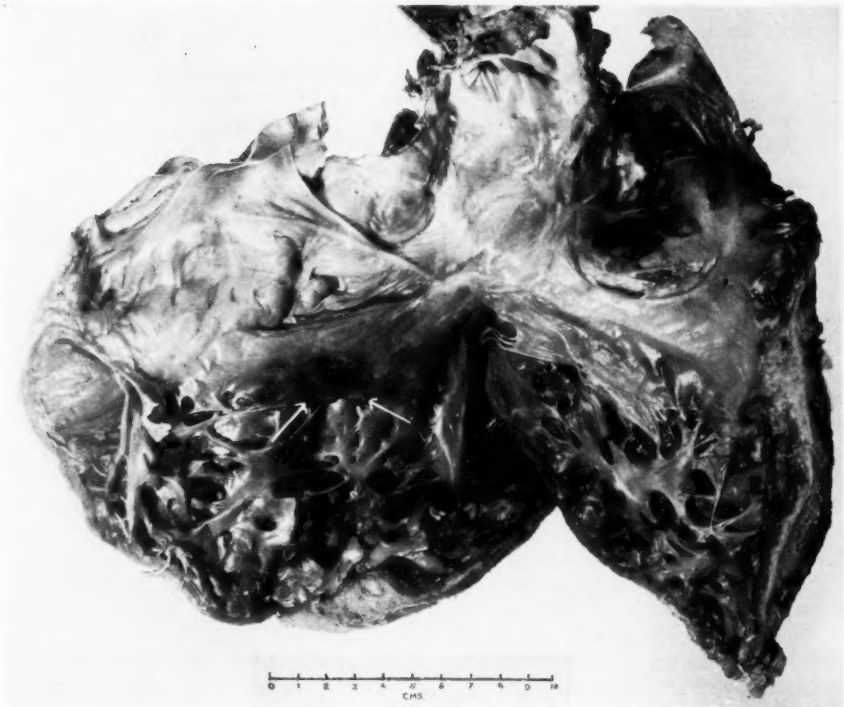

FIG. 3.—The dilated right ventricular cavity, showing the two cusps at the A–V orifice. The posterior cusp is seen to be tethered to the ventricular wall by short chordæ at its free margin.

arteriosus were closed. The aorta was somewhat hypoplastic and showed a few patches of fatty atheroma. The coronary arteries were free from atheroma. The pulmonary artery was of normal size and free from atheroma. The systemic veins were grossly dilated and tortuous veins formed a varicose plexus.

Histology of Heart. The pericardium showed fibroblastic proliferation with organization of the fibrinous exudate, but only minimal lymphocytic infiltration. There was severe venous and capillary congestion with numerous small hæmorrhages. The myocardium was normal. There were no Aschoff bodies or scars. The endocardium showed thickening of the mitral valve with normal arrangement of collagen fibres. The vegetations on the mitral and aortic valves and papillary muscles consisted of laminated thrombus which had undergone partial organization. The chordæ tendineæ were surrounded by concentric deposits of loose collagen. There were no inflammatory lesions either in the valves or the vegetations. No organisms could be seen in the vegetations.

Discussion

The earlier reports as reviewed by Herxheimer (1910) show confusion between incompetence of the valve and the Ebstein malformation. Abbott (1936) distinguished clearly between downward displacement of the valve (Ebstein's disease) and incomplete differentiation of the cusps leading to true incompetence, and describes one case of the latter. Other cases have been described by Hotz (1923), Ariel (1930), Dubin and Hollingshead (1944) and Palladino and Kinney (1948) who described two cases. Only one of these patients reached adult life. Of the cases described only two cusps were present in two instances, the cusps were tethered tightly to the ventricular wall in

three, and in four cases the cusps were misshapen with thickening and nodularity. The features of these examples and of the case now reported are summarized below.

PATHOLOGICAL FEATURES OF CONGENITAL TRICUSPID INCOMPETENCE

Author	Sex	Age	Number of cusps	Tethering of cusps	Thickening and nodularity	Condition of mitral valve
Abbott (1936)	M	7 days	3	No	Gross	Normal
Hotz (1923)	F	13 yr.	2	No	Present	Normal
Ariel (1930)	M	2 days	3	No	Gross	Grossly affected
D and H (1944)	F	5 min.	2	Yes	Slight	Normal
P and K I (1948)	M	34 yr.	3	Yes	Slight	Normal
P and K II (1948)	M	3 mth.	3	Yes	No	Normal
B and U (1956)	M	28 yr.	2	Yes	No	Slight nodular thickening

The diagnosis of this condition rests on the classical signs of tricuspid incompetence, the knowledge that a cardiac abnormality was present at an early age and the exclusion of the other causes of organic and functional tricuspid incompetence. In this case the physical signs were gross, the murmur was first heard at four years of age, and there was never any evidence of mitral stenosis or pulmonary hypertension. The cardiogram was characterized by right bundle-branch block; sinus rhythm later gave way to auricular fibrillation. Radiologically the striking features were progressive enlargement of the heart shadow which ultimately occupied almost the complete transverse diameter of the chest, and small pulmonary artery shadows. In spite of a steadily enlarging heart the patient remained relatively symptomless until the early twenties. Gross venous engorgement preceded the development of congestive failure by several years.

The cause of the lesion is generally ascribed to incomplete undermining of the primitive endocardial cushions by sinusoidal spaces which differentiate the cushions into cusps, chordæ tendineæ, and papillary muscles. The thickening and nodularity may be due to defective absorption of the substance of the cushions, but hyperplasia of the cushions has been suggested as an explanation.

Two other features of the case require comment. The endocardial vegetations appear to be due to a terminal non-infective deposition of endocardial thrombi found occasionally at autopsy on subjects debilitated by a prolonged illness (the "marantic thrombi" of older writers). The thickening of the chordæ tendineæ was shown to be due to recent deposition of collagen, almost certainly the result of organization of previous thrombi of the same nature. The pericarditis is more difficult to explain in the absence of rheumatism, tuberculosis, pyogenic infection or uræmia. It may possibly have been a reaction to extravasation of blood from grossly engorged coronary veins.

Summary

A case of congenital tricuspid incompetence is described and the previously reported cases are briefly reviewed.

We are grateful to Professor C. Bruce Perry, Dr. H. J. Orr-Ewing and Professor T. F. Hewer for permission to publish this case, and for their help and advice.

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BALL-THROMBUS OF THE RIGHT ATRIUM

BY

EVA FROMMER

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A study of reported cases reveals that while the occurrence of ball-thrombus of the left atrium is unusual a ball-thrombus of the right atrium is very rare indeed. The first case report is that of McLeod, in 1883, and sixty-one years elapse before the next—that of Wright, Flynn, and Druet, in 1944. Radding in America and Moia *et al.* in Argentina each published a report of a case in 1951, and the latter refer to an unpublished thesis by Romano of Buenos Aires (1944), in which a further case is described. As only five examples have apparenty been reported up to the present, it is thought of interest to record a sixth. On correlating the histories and clinical findings, a distinct picture emerges; indeed, it may be possible to make an ante-mortem diagnosis of ball valve obstruction of the tricuspid valve, as actually occurred in the case of Wright *et al.* (1944); whether or not it is due to a thrombus, however, and whether this thrombus is free or attached, cannot be clinically ascertained.

Case Report

The patient, a woman of 69, was admitted on 16/7/54, complaining of breathlessness and nausea. She had been quite healthy in the past, apart from occasional fainting attacks and some winter bronchitis, and had had ten normal pregnancies. Five years previously she was told that she had a murmur in the heart and was given a short course of tablets. Thirteen months previously she had a severe attack of breathlessness on rising in the morning lasting three to four hours. Since this time she had been unable to lie flat. A similar attack occurred one month before admission and she had stayed in bed since this. Nausea set in two weeks, and peripheral œdema one week, before admission.

On examination she was a pale, dyspnœic, rather nervous woman. She had a regular pulse, slowly rising in quality, and marked arteriosclerosis. Her blood pressure was 190/85. The apex-beat was in the left sixth space in the anterior axillary line, and heaving in quality. There were no thrills. A rough systolic murmur was heard in the aortic area, with an early diastolic murmur of aortic regurgitation which was conducted down the left border of the sternum. There was also a loud mitral systolic murmur. The abdomen was distended, the liver not palpable, and there was pitting œdema of the legs and sacrum. In the chest there was poor air-entry, with generalized crepitations over both lower lobes, and signs of fluid at both bases, more on the right.

A diagnosis of aortic stenosis with incompetence and left ventricular failure was made.

Results of Investigations. X-ray of chest (one week after admission): gross cardiac enlargement, unfolded and elongated aorta, right basal effusion. Radioscopy (two weeks after admission): transverse heart, enlargement of left ventricle with full pulsation; full, kicking pulsation of tortuous aorta, no calcium seen; moderate enlargement of right ventricle; enlargement of left atrium.

Electrocardiogram. Left ventricular hypertrophy.

Treatment and Progress. The patient was put on a salt-free diet, and given digoxin, neomercazole, and mersalyl; she was also given a course of chloramphenicol. The response initially was good, except for persistent nausea, and orthopnœa. On 2/8/54 the patient had a blackout in the evening and from that time her condition deteriorated.

On several occasions she complained of throbbing in the abdomen in the evening. During one such episode there was marked distension of the peripheral veins, down to the dorsum of the hand, lasting about

an hour, with moderate dyspnœa of air-hunger type. This symptom was not properly evaluated at the time but the patient remarked that she had noticed the venous distension before.

On 22/8/54 the right pleural effusion reappeared. On 31/8/54, 580 ml. of sterile, bloodstained fluid were aspirated from the right side of the chest, there was no symptomatic relief. The patient developed a purpuric rash, became comatose, and died on 4/9/54.

Necropsy (6/9/54: Dr. S. Robinson). Ball-thrombus in right auricle; failure of hypertrophied left ventricle; calcification and stenosis of aortic valve; chronic rheumatic endocarditis.

Weight of heart 660 grammes. Foraman ovale closed. Œdema, cloudy swelling, and very great hypertrophy of myocardium of left ventricle. (Left ventricle 2 cm., right ventricle 0·5 cm. thick.) Several discrete masses of ante-mortem thrombus (up to 1 cm. diameter) enmeshed in columnæ carneæ at apex. Slight hypertrophy of right auricle with polypous mass (2·5×2×1 cm.) of furrowed, reddish-grey ante-mortem thrombus adherent to endocardium of appendix; ball-thrombus 3×3×2 cm. lying free in cavity of right auricle, with irregular, partly furrowed, mottled red and white outer surface, with short projections up to 1 cm. long, and diffluent reddish-grey centre. Severe fibrosis with calcification and stenosis of aortic valve; other valves normal. Slight atheroma of coronary arteries; severe atheroma of aorta and its branches with ante-mortem thrombus lining upper abdominal aorta and blocking cœliac axis.

The lungs showed red induration with hæmorrhagic infarction of lower lobe of right lung and ante-mortem thrombus in right pulmonary artery. Collapse and similar infarction (2×2 cm.) in lower lobe of left lung. Hæmorrhagic effusion (500 c.c.) in the right pleural cavity.

Great congestion of abdominal organs and brain.

Massive general anasarca; ecchymoses on arms, knees, and right foot of a cyanosed, well-developed, moderately well-nourished woman.

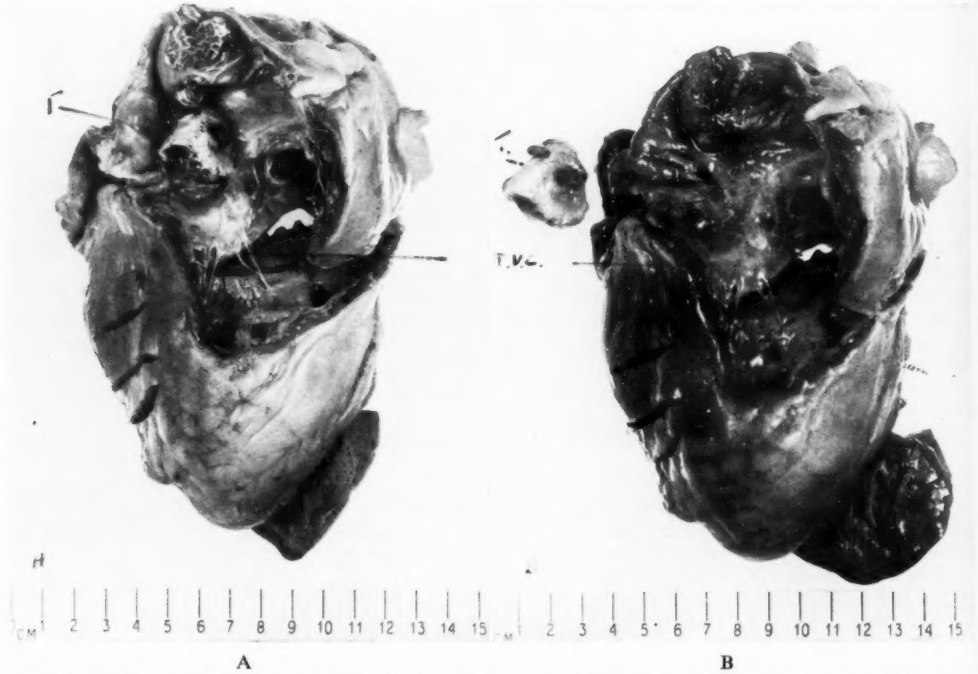

FIG. 1.—Heart opened at necropsy; right anterior wall removed. (A) Showing thrombus *in situ* (T). (B) Showing the detached thrombus (T) which has lost its rounded contour in fixing. The septal cusp of the tricuspid valve (TVC) is seen.

Discussion

Wright *et al.* in their case report set out the criteria on which they were able—before the patient's death—to make their diagnosis of a movable embolus riding over the tricuspid valve.

A composite picture emerges from previous reports and this case, of a patient who may have a known valvular lesion, with congestive failure, or who has recently suffered a severe disease, who suddenly develops a syncopal attack without any obvious cause, and with marked air-hunger, despite a good air-entry into the chest. Severe orthopnœa develops, out of proportion to the degree of cardiac failure, and there may be pain in the chest aggravated by lying back. Intractable nausea sets in. There are attacks of dyspnœa, often accompanied by great engorgement of the peripheral veins, which even pulsate in some instances down to the long saphenous. The liver during these bouts, or at other times, becomes engorged and pulsates.

The condition is necessarily progressive, and the outcome fatal, but the mobility of the ball-thrombus within the atrium causes striking variations in both symptoms and signs through its erratic behaviour. Episodes of almost complete obstruction of the pulmonary blood-flow can alternate with periods of freedom, producing rapid changes in the state of the lungs. In other cases intermittent incompetence of the valve through partial impaction of the thrombus in it, may complicate the clinical picture. The size of the thrombus and the state of the valve also affect this.

Summary

A case of ball-thrombus in the right atrium of a patient with rheumatic aortic stenosis and incompetence is described. A consideration of the symptomatology suggests that a diagnosis of this condition can be made during life, by the presence of intermittent symptoms and signs of tricuspid stenosis.

I wish to express my gratitude to Dr. H. E. S. Pearson for permission to publish this case, and for his help and encouragement and also to Dr. S. Robinson for the post-mortem report and photographs, and for valuable criticism.

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ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

The Mechanics of Pulmonary Ventilation in Patients with Heart Disease. C. C. BROWN, D. L. FRY, and R. V. EBERT. *Amer. J. Med.*, **17**, 438–466, Oct., 1954.

The authors have carried out a study at the University of Minnesota Medical School, Minneapolis, of the mechanics of ventilation, with particular reference to the cause of dyspnœa in patients with heart disease. Their method was based on the theory that the intrathoracic pressure at any time during breathing represents the sum of (1) the retractive forces of the lungs, (2) the pressure required to overcome tissue friction of the lung, and (3) the pressure gradient required to produce a flow of air through the bronchial tree. Intrathoracic pressure was measured by means of a balloon in the œsophagus, the difference between this pressure and that in the mouth being recorded by a differential strain gauge. The breathing was interrupted suddenly at any point by either a hand-operated three-way respiratory valve or an electrically operated solenoid valve. A spirometer tracing of the changes in lung volume was made. To differentiate between the pressure required to overcome tissue friction of the lung and the pressure gradient required to maintain the flow of gas through the bronchi it was necessary to make the subjects breathe two gases with different physical properties but about equal kinematic viscosity; those chosen were air and a mixture of oxygen (20%) and argon (80%). The increase in lung volume was plotted against the static intrathoracic pressure in order to produce a pressure-volume curve for each subject.

In all, 10 normal men, 6 normal women, and 16 patients of both sexes with heart disease, mainly rheumatic, were examined. It was found that the pressure required to produce a change in lung volume of 100 ml. was significantly greater in patients with heart disease. This factor was found to show a high degree of correlation with the reciprocal of the vital capacity both of normal subjects and of patients, but no relation was found between the reduction in vital capacity and the increased resistance to air flow.

Comparison of the pressure-flow relationships in patients with heart disease when breathing the two gas mixtures showed that tissue friction was a negligible factor and that the degree of movement of the lungs was determined by the degree of resistance to gas flow. Since there may be no increase in resistance to air flow in patients with heart disease and exertional dyspnoea the authors conclude that the latter is most closely related to a reduction in vital capacity and to the altered elastic properties of the lung; on the other hand it is thought likely that increased resistance to air flow may play an important role in the dyspnœa of cardiac asthma.

H. E. Holling

A Manual on Cardiac Resuscitation. R. M. HOSLIER Oxford: Blackwell Scientific Publications. Pp., x+ 183. 30*s*.

This small handbook on cardiac resuscitation, based on the course given at Cleveland, Ohio, is designed to provide the anæsthetist and surgeon with the knowledge that will enable them to treat promptly and efficiently a case of cardiac arrest occurring under anæsthesia. After introductory chapters on the physiological aspect of cardiac arrest, predisposing factors, and preventive measures, the rest of the book is devoted to a detailed and practical description of a two-part plan for restoring the normal circulation, the first being the re-establishment of the " oxygen system " and cardiac massage, and the second the treatment of cardiac standstill in ventricular fibrillation. The author claims that if the plan is properly carried out any normal heart that has stopped can be made to beat again.

Graham Hayward

Peripheral Vascular Diseases (2nd Edition). WILLIAM S. COLLENS, M.D., and NATHAN D. WILENSKY, M.D. Oxford: Blackwell Scientific Publications, 1953. Pp. 622. Fig. 226. 86*s*.

The scope of the book has been widened since the first edition appeared fourteen years ago, as in addition to an extensive revision of the original text there are descriptions of the vascular disorders of the skin, brain and spinal cord and viscera. The wisdom of including a chapter on the vascular diseases of the brain is doubtful as it is so short as to be of little value to either the physician interested in peripheral vascular disorders, as they are usually understood, or to the neurologist. The early part of the book consists of chapters on methods of examination and on the different vascular diseases. Nearly two-thirds of the book is devoted to treatment and the dust cover claims that every known method of treatment is included. There are full and practical descriptions of medical, surgical, and physical methods of treatment but the absence of any cross references in the text necessitates frequent use of the index if the treatment of any particular disorder is sought. The value of the book for reference purposes is limited by the inadequacy of the index which is incomplete and so arranged that it is difficult to find any particular piece of information.

Graham Hayward

Atlas Postmortaler Angiogramme. J. SCHOENMACKERS and H. VIETEN. Stuttgart: Georg Thieme, Verlag, 1954. Pp. 203; Illus. 131. D.M.57.

This atlas is based on 131 angiograms obtained at necropsy by injection of arteries, or in some cases veins, with radio opaque materials. The reproductions are excellent and

in addition to a full description in the text there are summaries in English, French, and Spanish at the end of each chapter. A large number of the illustrations were obtained from patients with disease of the heart or lungs and the sections on acquired heart disease, due to hypertension, coronary disease, or mitral stenosis, or on the various types of congenital heart disease, will be of great interest to the cardiologist. Other chapters illustrate the changes in the blood vessels of the kidneys in various diseases and in the portal circulation in portal hypertension and cirrhosis of the liver. This book should be studied by all who are interested in the study of the circulation by means of the injection of radio-opaque substances. *Graham Hayward*

Practical Electrocardiography. HENRY J. L. MARRIOTT, M.D. London: Baillière, Tindall & Cox. Pp. xii+ 172 with 115 illustrations.

In his preface the author states that " books on electrocardiography seem to possess one or more of several disadvantages for the beginner "; this book is no exception. We are told that introductory chapters on electrophysiology are often too intricate, but they may be so brief that electrocardiography becomes an empirical interpretation of patterns without rationale. We are told that in some books " only certain aspects of the subject are dealt with, for example, the arrhythmias may be entirely omitted "; in this book there is very little mention of the electrocardiographic findings in angina pectoris. Two pages are devoted to coronary insufficiency.

The author has endeavoured to present an easy technique of interpreting electrocardiograms. This is partially achieved but interpretation is surely confused by indiscriminate use of V leads and CF leads to illustrate the præcordial electrocardiogram. Your reviewer agrees that it is useful to take advantages of the " emphasizing tendencies of the CR and CF connections, rather than to rely slavishly on the V leads because they are theoretically superior," but the auricular arrhythmias are not illustrated by CR1, which is especially useful in emphasizing P waves and CF leads appear too frequently in the illustrations.

This book is profusely illustrated and the author has achieved his object of presenting the pictures adjacent to the relevant text. However, many of the electrocardiograms are poorly reproduced and many are indifferent examples from the technical point of view. It is difficult to understand why chapters concerned with myocardial pathology, such as ventricular hypertrophy and myocardial infarction are separated by sections on the arrhythmias. This book is not burdened by an extensive bibliography but there is an index to illustrative electrocardiograms and a general index. *Wallace Brigden*

Post-mortem Studies on Coronary Atherosclerosis, Serum Beta Lipoproteins and Somatotypes. D. M. SPAIN, V. A. BRADESS, and I. J. GREENBLATT. *Amer. J. med. Sci.*, **239**, 294–301, March, 1955.

In continuation of a previous investigation (*Ann. intern. Med.*, 1952, **38**, 254; *Abstracts of World Medicine*, 1953, **14**, 216) the authors have carried out, at the Beth-El Hospital, Brooklyn, New York, a post-mortem study of the relationship between the serum beta-lipoprotein level, the somatotype of the patient, and the degree of coronary atherosclerosis in 157 apparently healthy persons who died suddenly from accident, suicide, homicide, or coronary occlusion; somatotypes were determined according to Sheldon's methods. In most of the cases blood for analysis was obtained within six hours after death.

Of the 157 subjects, 73 died suddenly from coronary accident, and in 58 of these there was an abnormal beta-lipoprotein pattern. The over-all coefficient of correlation between the serum beta-lipoprotein pattern and the degree of coronary atherosclerosis was 0·84. When the cases were classified by somatotype the correlation for the mixed group of mesomorphs and endomorphs was 0·91, whereas for the group consisting of ectomorphic males it was only 0·6. The authors conclude from this study that " any male or female, with the exception of the ectomorphic male, who has an abnormal serum beta-lipoprotein pattern must be seriously regarded as a potential victim of atherosclerosis. This is particularly true of the mesomorphic male." *Z. A. Leitner*

Objective Evaluation of Coronary Vasodilator Drugs. H. I. RUSSEK, B. L. ZOHMAN, and V. J. DORSET. *Amer. J. med. Sci.*, **229**, 46–54, Jan., 1955.

The efficacy of supposed coronary vasodilator drugs was studied by observing whether they modified the electrocardiographic response to a standard Master two-step exercise test. The ability of these drugs to relieve pain on exertion was not primarily considered. The patients selected included 60 with coronary disease in whom, on repeated testing under identical conditions, there was a relative constant positive electrocardiographic response to exercise which could be favourably modified by a sublingual dose of glyceryl trinitrate taken just before the test (glyceryl trinitrate being accepted as a potent coronary vasodilator). Of all the drugs tried, only two in addition to glyceryl trinitrate gave responses which justified their use in the management of angina pectoris. Thus papaverine, 1 to 2 gr. (0·06 to 0·13 g.) intravenously or 3 to 8 gr. (0·2 to 0·52 g.) by mouth, was effective in 14 out of 24 patients, but was ineffective in the usual therapeutic dosage. The only drug that was of any value for more prolonged prophylaxis was pentaerythrityl tetranitrate (" peritrate "), 10 to 20 mg. having a marked effect for 4 to 5 hours by this test. *J. N. Agate*

Herzkrankheiten im Säuglingsalter. Von Priv.-Doz. Dr. E. ROSSI, Zürich. Mit einem Geleitwort von Prof. Dr. G. FANCONI, Zürich. 1954. XVI, 373 Seiten, 198 teils mehrfarbige Abbildungen in 369 Einzeldarstellungen und 1 Ausschlagtafel „ Differentialdiagnose der wichtigsten kongenitalen Angiokardiopathien „, Gr.-8⁰, Ganzleinen DM 65.

" Heart Disease in Infancy " is based on the study of some hundred cases seen at Zurich. The first chapter is of practical use for therein we find many valuable facts about the normal findings of the heart at this age.

Englargement of the heart as a result of various congenital defects comes next. In fact it is from the point of view of enlargement that all these developmental errors are considered. Whether this is really a good approach is perhaps doubtful, although naturally in some ways this secondary effect does gauge the severity of the defect. The third chapter is more interesting as it deals with the myocardial defects. There " enlargement " is considered as it occurs apart from the malformation. Two more chapters deal with causes of enlargement as a consequence of primary extracardiac diseases, and with treatment. This is a good book with plenty of information. The matter is well arranged and illustrated by diagrams, many in colours. There are plenty of references, and numerous photomicrographs and pictures of specimens. One hundred and sixty-one case histories are included. An amazing amount of knowledge has accumulated about heart disease in infancy; my 1924 edition of Von Reuss has only ten pages. *Terence East*

Probleme und Beispiele biologischer Regelung. R. WAGNER. 1954. Georg Thieme Verlag, Stuttgart. 219 pages, 38 illustrations. 29.40 DM.

This is a physiological study of the problems of biological control. The author first discusses the mechanism of the control of voluntary movement. The second main part of the book considers the mechanism of the control of the circulation. First comes the regulation of the level of the blood pressure, and the control of the heart. The author thinks that the methods of control of voluntary movement and those of the circulation have much in common. Such an integration is always welcome as a move towards simplicity; but here the expression hardly merits that quality. There are whole pages unbroken by any paragraphs, which make reading heavy. Anyone who is prepared to tackle this philosophical physiology will no doubt find something interesting. *Terence East*

Acetazoleamide (Diamox) Diuresis. A. RUSKIN. *Arch. intern. Med.*, **95**, 24, 1955.

Working at the University of Texas, Galveston, Texas, the author has studied the diuretic effect of acetazoleamide (" diamox ") when given orally to patients with and without heart failure in doses ranging from 500 mg. to 6 g. in 24 hours. With large doses the urinary volume was more than doubled in 24 hours, accompanied by a marked rise in sodium and potassium excretion. The diuresis lessened on the following day, but electrolyte excretion continued in large amounts. In some cases diuresis and weight loss continued for periods up to 3 weeks without further administration of diuretics. Toxic effects were mild paræsthesiæ, drowsiness, nausea, vomiting (in 3 out of 15 cases), and the occurrence of a reversible psychosis in one patient with nephrosclerosis and uræmia. In 12 patients with heart failure receiving either a single dose or repeated dosage (500 mg. of diamox at 8-hourly intervals for 4 doses) diuresis was only slightly more effective in the second and third 8-hour periods, but with repeated dosage sodium excretion was more effective during the 24 hours and the following day than with the single dose.

Acetazoleamide diuresis is attributed to the inhibition of carbonic anhydrase in the renal tubules, producing an alkaline urine and excessive distal tubular excretion of potassium, with a decreased tubular reabsorption of sodium, bicarbonate, and consequently of water.
I. Ansell

The Nature of Spontaneous Auricular Fibrillation in Man. With Comments on the Action of Antiarrhythmic Drugs. M. PRINZMETAL, L. RAKITA, J. L. BORDUAS, E. FLAMM, and A. GOLDMAN. *J. Amer. med. Ass.*, **157**, 1175–1182, April 4, 1955.

The exact mechanism of auricular fibrillation in man has never been satisfactorily demonstrated. As a contribution to this subject the authors took the opportunity during the surgical treatment of patients with mitral stenosis and auricular fibrillation at the Cedars of Lebanon Hospital, Los Angeles, to obtain direct electrocardiograms from the fibrillating auricles and also to make high-speed cinematographic records.

By neither method was any evidence adduced for the " circus movement " postulated by Lewis. The electrocardiograms showed large waves occurring irregularly at a rate of 250 to 400 per minute, with in addition highly irregular small waves along the base line. It has been shown previously that auricular flutter is due to the presence in the auricle of a rapidly discharging ectopic focus, and that auricular tachycardia, auricular extrasystoles, and auricular flutter are essentially of the same nature, in that the contraction pursues an orderly course from the site of origin to the extremities of the auricles. It is argued that if the rate of contraction of the ectopic focus exceeds a critical threshold—which varies in different patients—there is a complete breakdown of orderly mechanical and electrical activity, and auricular fibrillation results. This has been experimentally demonstrated on the heart of the dog.

The application of these findings to treatment is considered, and in a discussion of the action of drugs it is suggested that if the action of quinidine is gradually to slow the rate of discharge from an ectopic focus all the effects of this drug in varying doses can readily be explained. It is considered probable that procaine amide acts similarly. *C. Bruce Perry*

Acute, Fatal Myocarditis. Clinical-pathological Analysis of 15 Cases of Fatal Myocarditis and Some Diagnostic and Therapeutic Considerations. [In English.] K. GYDELL, G. BJÖRCK, and S. WINBLAD. *Acta med. scand.*, **151**, 1–17, Feb. 8, 1955.

The clinical features and necropsy findings in 15 cases of myocarditis, seen for the most part at Malmö General Hospital, Sweden, between 1944 and 1952, were analysed. The cases were divided into two groups according to the necropsy findings: (1) rheumatic myocarditis, in which Aschoff granulomata were found (7 cases); and (2) non-rheumatic myocarditis, in which non-specific inflammatory changes were noted (8 cases). Cardiac enlargement was present in all except two.

The most frequent electrocardiographic changes

were abnormalities in the S–T segment and T waves. In several of the cases of non-rheumatic myocarditis the condition was not diagnosed during life. The authors point out that in these cases sudden death may follow an apparently mild infection of the respiratory tract, such infection being apparently the commonest associated cause of death.

It is believed that the incidence of acute myocarditis is decreasing, perhaps as the result of the use of antibiotics in respiratory infection; if, however, such an infection does not respond to antibiotics the possibility of myocarditis as a complication should be considered, and serial radiographs and electrocardiograms should be examined. Rheumatic myocarditis is generally more readily diagnosed than the non-rheumatic form because the patient's history is suggestive. The authors advise retaining the term myocarditis for a wide variety of infections and hyperergic, allergic, toxic, and metabolic conditions in order to emphasize the " structural lesions of myocardial cells " (apart from ischæmic heart disease) " resulting in impairment of cardiac function."

R. S. Stevens

Surgical Treatment of Forty-six Interatrial Septal Defects by Atrio-septo pexy. C. P. BAILEY, H. T. NICHOLS, H. E. BOLTON, W. L. JAMISON, and H. GOMEZ-ALMEIDA. *Ann. Surg.*, **140**, 805–820, Dec., 1954.

The operation of atrio-septo-pexy as originally devised consisted in closing an atrial septal defect by suturing an invaginated portion of the right atrial wall to the margins of the defect. Increasing experience has shown, however, that if the defect is large there may not be a complete rim of septal tissue, and complete closure by this method may not be possible. Recently the authors have come to the conclusion that closure is not necessary so long as the systemic and pulmonary venous systems can be separated. In some cases this problem has been solved by suturing the atrial wall to the free edge of the posterior septal remnant, thus converting the right atrial cavity into a U-shaped chamber lying behind the defect. (This modification has been named the " Pompeian version of atrio-septo-pexy," by analogy to the ancient Pompeian method of manufacturing water-pipes.) The modified operation is very satisfactory in patients with a persistent remnant of lower septal tissue, but is not so suitable when the septum primum is totally absent, whether or not a septum secundum is present. Attempts to apply the technique in such cases may lead to damage to the bundle of His as it runs along the free upper margin of the muscular part of the interventricular septum. In these cases it is safe to complete the intracardial channel except for a short interval between the upper lip of the ostium of the coronary sinus and the most anterior (membranous) portion of the interventricular septum; the residual gap may then be closed with a small bag of pericardial fat placed on the left atrial side of the defect after carrying out Kiriluk's technique.

Anomalous pulmonary venous return may be dealt with at the same operation. If only one vein empties abnormally it may be re-implanted into the side of the normally emptying vein. However, if both right pulmonary veins drain into the right atrium they may be excluded by suturing the lateral atrial wall to the anterior margin of the septal defect, thus converting the right atrium into two compartments, of which the small posterior one drains the right pulmonary veins directly into the left atrium.

The authors believe that the closed technique is better than an open method at the present time, and that hypothermia gives no added advantage, especially in adults. A total of 46 patients have so far been operated on. Among 30 patients with septum secundum atrial defects there were 3 operative deaths, but all the survivors showed marked clinical improvement, with complete abolition of the shunt in the majority. Among the 16 patients with ostium primum septal defects there were 11 operative deaths.

In conclusion the authors state their belief that correction of an interatrial communication is not indicated in patients with a right-to-left shunt.

F. J. Sambrook Gowar

The Cardiovascular Aspects of Marfan's Syndrome: a Heritable Disorder of Connective Tissue. V. A. MCKUSICK. *Circulation (N.Y.)*, **11**, 321–342, March, 1955.

Marfan's syndrome is characterized by a wide variety of abnormalities which may be present in different combinations. The commonest abnormality is congenital dislocation of the lens, others being unusual length of limb with poor muscular tone, arachnodactyly, talipes, pes planus or syndactyly, herniæ, high-arching palate, and kyphosis causing either pigeon-breast or pectus excavatum.

In this paper from the Johns Hopkins University and Hospital the author discusses the cardiovascular abnormalities. These generally affect the ascending aorta, causing fusiform aneurysm, dissecting aneurysm, and dilatation of the aortic ring with aortic incompetence. Any of these may directly or indirectly cause death, possibly suddenly, in children or young adults. Less commonly there may be minor degrees of coarctation of the aorta, patent ductus, atrial septal defect, dilatation of the pulmonary artery, and mitral-valve deformities, which last may be complicated by bacterial endocarditis. It seems likely that the diagnosis of Marfan's syndrome may be overlooked in cardiac patients in whom the significance of abnormalities elsewhere in the body is not appreciated.

The author suggests that the underlying abnormality in all lesions may be an abiotrophy of connective tissue, causing disruption of elastic fibres which may not become evident until late childhood or adult life. In a study of the familial aspects of the condition he traced 50 families in which there was one certain instance of Marfan's syndrome; in 70 per cent of the families there were other certain or possible cases. The total number of definitely affected subjects was approximately 105, and in 46 of these the cardiovascular system was involved.

J. A. Cosh

The Use of Simultaneous Left Heart Pressure Pulse Measurements in Evaluating the Effects of Mitral Valve Surgery.—H. L. MOSCOVITZ, A. J. GORDON, E. BRAUNWALD, S. S. AMRAM, S. O. SAPIN, R. P. LASSER, A. HIMMELSTEIN, and M. M. RAVITCH. *Amer. J. Med.*, **18**, 406–414, March, 1955.

During the operation of mitral valvotomy on 7 patients at Mount Sinai Hospital, New York, the pressure gradient across the stenosed mitral valve was determined by simultaneous measurement of the left atrial and left ventricular pressures, No. 20 needles being inserted into the left atrium, the left ventricle, and the aorta and being connected to three matched strain-gauge manometers by sterilized vinyl tubing.

The difference in filling pressure across the healthy mitral valve is normally too small to be measurable, but when the valve is stenosed the pressure gradient may rise to 20 mm. Hg. A more accurate assessment of the changes in filling pressure under different conditions would be aided by the simultaneous measurement of cardiac output, but so far the authors have not found it possible to do this under the conditions obtaining in the operating theatre. They point out that the performance of valvotomy is accompanied by a reduction in the pressure gradient which is correlated with the adequacy of the surgical procedure. In all cases the reduction in the pressure gradient is mainly due to a reduction in left atrial pressure, but in a few cases an elevation of left ventricular diastolic pressure also occurs. The authors suggest that measurement of the pressure gradient during the course of a valvotomy provides an estimate of the likely extent of the residual stenosis and is thus of help in deciding whether the attempt to increase the valve opening should be continued. *H. E. Holling*

Results of Radical Pericardiectomy for Constrictive Pericarditis. E. HOLMAN and F. WILLETT. *J. Amer. med. Ass.*, **157**, 789.

In reporting their experiences of the treatment of constrictive pericarditis the authors stress the need for more radical surgery in this condition, regarding delay in improvement and need for a second operation as due to inadequate pericardiectomy. They consider that when calcification is present, even if symptoms are mild, decortication should be performed, as cardiac disability is progressive. In tuberculous pericarditis decompression of the heart by aspiration or operation is indicated as soon as symptoms of compression appear. The operation they use is as follows. The pericardium is excised to beyond the left, right, and the inferior borders of the heart, and often over the venæ cavæ at the base. A mid-line incision is made, with vertical division of the sternum, which is repaired with at least three steel stitches over which the pectoral fascia is reapproximated. The decortication is begun over the apex and the left side liberated first, excising through a plane just outside the muscle, sometimes in two layers. If the heart is irritable and becomes irregular, there should be a few moments' delay. Hæmorrhage from the heart can be controlled by stitching down a small flap of the mobilized pericardium. The mediastinum and the right pleural cavity are drained. Full chemotherapy is given before and after operation.

The authors have performed this operation on 26 patients with constrictive pericarditis, the oldest aged 55. There were no operative deaths, but 4 patients died subsequently, 2 from myocardial failure and 2 from unrelated causes. The other 22 patients—8 with tuberculous and 14 with non-tuberculous pericarditis—are all well although 3 in each group have some limitation of activity. *M. Meredith Brown*

Staphylococcal Endocarditis. Some Clinical and Therapeutic Observations on Thirty-eight Cases. A. M. FISHER, H. N. WAGNER, and R. S. ROSS. *Arch. intern. Med.*, **95**, 427–437, March, 1955.

The authors describe the results of treatment in 38 cases of staphylococcal endocarditis at Johns Hopkins Hospital, Baltimore. These fell into three groups: (I) 22 cases treated before antibiotics became available; (II) 3 cases treated between 1944 and 1948, when effective doses of penicillin were used and most strains of staphylococci were sensitive to the drug; and (III) 13 cases treated in the period 1949–53. Of the total number, the pre-existing heart disease was congenital in 10, rheumatic in 9, and hypertensive-arteriosclerotic in 6; in 13 there was no pre-existing cardiac condition. All but one of the 22 patients in Group I died, treatment in the successful case being with sulphanilamide, antiserum, and blood transfusion; in Group II there were two deaths and one recovery; while in Group III 6 patients survived and 7 died.

The authors discuss problems in diagnosis and treatment, mostly on the basis of the 13 cases in Group III.

The bactericidal and bacteriostatic effect of the patient's serum in different dilutions against the infecting staphylococcus is considered to be a useful guide to therapy. For testing the sensitivity of the staphylococcus to various antibiotics as well as to penicillin the tube dilution test was found to be more satisfactory than the disk method.

The authors conclude that in cases of bacterial endocarditis, even when there are indications that the organism is resistant to the drug, penicillin should always be given in doses ranging from 8 to 24 mega units a day. Erythromycin in large doses—up to 3·6 g. a day for five weeks—may also be given, with one of the broad-spectrum antibiotics in addition. As regards length of treatment, the authors state that they "would hesitate . . . to advocate stopping (treatment) any sooner" than before the 6th or 7th week. *G. S. Crockett*

Acute Pulmonary Edema. MARK D. ALTSCHULE, M.D. New York: Grune & Stratton. 1954. Pp. ix+68. 28*s*.

In this short monograph the author discusses those physiological factors that are thought to influence the formation of œdema fluid in the lung. The pathological physiology of human acute pulmonary œdema is described very briefly and a rather inadequate account of present views is given on the pathogenesis of pulmonary œdema due to cardiovascular disease. The chapters on clinical manifestations and treatment add little to the information already available in the standard textbooks. *Graham Hayward*

THE NORMAL BALLISTOCARDIOGRAM

BY

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Received March 16, 1955

The use of ballistocardiography in clinical practice has been greatly simplified by the introduction by Dock and Taubman (1949) of the direct pick-up which can be used in home or hospital. Each type of instrument has its own physical characteristics, and criteria for normality have to be defined for each. Brown *et al.* (1952) working with the high-frequency table ballistocardiograph emphasized that the systolic waves must be constant in form and uniform in duration, and classified degrees of abnormality as follows.

Grade 1. Complexes normal in form; the expiratory amplitude less than half that of inspiration.
Grade 2. Decrease in inspiratory amplitude; half or more of the complexes abnormal.
Grade 3. Complexes identifiable but variable; abnormalities present throughout.
Grade 4. Complexes small, irregular, and unidentifiable.

Dock *et al.* (1953), who use a direct body pick-up, allow a minority of abnormal complexes in Grade 1, and group with Grade 2 those tracings with marked respiratory variation in which the smaller complexes outnumber the larger. An abnormal pattern is defined as one in which the depth of the first downstroke is less than one-tenth of the height of the main systolic upstroke, the amplitudes of the H and K waves are respectively over 50 and 80 per cent of that of the J wave, or the upward diastolic deflections are larger than the systolic ones. Scarborough *et al.* (1953), with a high-frequency table, found no definitely abnormal ballistocardiograms in 137 healthy persons aged twenty to forty. Using a photo-electric apparatus, Pordy *et al.* (1951) found only 3 abnormal in 44 normal subjects under fifty. The incidence of abnormality increased with age in both groups.

Abnormalities in the ballistocardiogram have been made the basis of far-reaching conclusions. Henderson (1953) considered changes in wave form after smoking evidence of the deleterious effect of tobacco on the myocardium. Brown *et al.* (1950) regarded a normal tracing as strong evidence against the presence of angina pectoris. Starr (1947) concluded from an 8–10 year follow up of 90 healthy subjects that abnormalities in the older age group are associated with a high incidence of cardiovascular disease and considered (1952) finding an abnormal tracing in an apparently healthy subject sufficient to warrant modification of the person's way of life.

The present study was undertaken in order to re-assess the criteria for normality in the light of these claims.

Methods and Materials

Ballistocardiograms of 200 subjects between 14 and 65 years of age were recorded, using a Sanborn photo-electric direct body pick-up and a Sanborn Polyviso 4-channel recorder. The first hundred were drawn from students, doctors, and technical staff, and the remainder from patients without cardiac disease or any condition, such as thyrotoxicosis, known to affect the ballistocardiogram. Some diabetics and a few very mild asthmatics in a quiescent phase were included. No abnormality was found in any subject on clinical, electrocardiographic, or radiological examination. No patient had a blood pressure of over 170/100 mm.

The ballistocardiogram was recorded at least two hours after a meal. Smoking was forbidden for the previous hour and any exertion for the previous fifteen minutes. No patients were taking any drugs with an action on the heart.

When the effects of respiratory distortion are eliminated by use of a filter, some means of distinguishing between complexes produced during inspiration and expiration become necessary. Initially, simultaneous pneumograms were recorded, using a rubber catheter inserted into one nostril and connected to a Sanborn electromanometer. It was later found that with the subject breathing quietly through his mouth and his head resting on a large, soft pillow, respiratory movement was detectable, but distortion minimal even without the filter, so that the pneumogram became unnecessary. Even when the unfiltered records were not wholly satisfactory, they could be used to identify the inspiratory and expiratory complexes in the filtered record.

In 79 subjects, the sensitivity of the recorder was standardized so that 1 mv. produced a 1 cm. deflection; in the remainder it was adjusted so as to give the most satisfactory wave form. Tracings were taken with the subject lying either on the floor or on a built-in laboratory bench. Vibration of the building did not constitute a problem.

Insufficient emphasis has been laid on the practical difficulties inherent in ballistocardiography. A degree of patient co-operation comparable to that required for an estimation of the basal metabolic rate is needed. An unsatisfactory tracing may result from lack of co-operation, inability to lie flat or to relax, involuntary leg movements, and local conditions making resting of the crossbar squarely across the shins impossible. Of 100 patients, selected at random, to be assessed for suitability for ballistocardiographic examination, 16 were found to be temporarily and 25 permanently unsuitable, the reasons ranging from severe orthopnœa to a leg amputation.

The grosser departures from normal are associated with an irregular, non-repetitive trace without clearly identifiable complexes, so that a Grade 3 or 4 ballistocardiogram gives a superficial impression of being a technically poor tracing. However, observations on the effect on the normal ballistocardiogram of deliberately produced muscle tension, foot movement, and involuntary tremor resulting from fatigue showed that it was not possible to reproduce any of the pathological forms. The complexes, though often impossible to interpret owing to distortion, remained clearly distinguishable and there were marked deviations in the base line, which remained level in an abnormal but technically satisfactory tracing.

A number of tracings had to be rejected in the light of these findings as technically too poor to be interpreted, the figure of 200 for the series being reached after this elimination. Faulty recording was almost always associated with visible body and leg movement or obvious irregularities in the movement of the light beam, as seen in the window of the photo-electric cell.

Results

Applying Dock's criteria, 128 were found to be normal (Fig. 1), 23 to show a Grade 1, 2 a Grade 2, 4 a Grade 3, and 1 a Grade 4 abnormality: the remaining 44 did not fit into any of these groups. Category 1 in Tables I and II included 32 who were normal apart from an excessively large K wave, whose size in relation to the J wave varied between 0·8 : 1 and 1·5 : 1. It was often the dominant downward stroke and occasionally the most prominent stroke of the whole complex (Fig. 2): it varied in shape, being pointed, rounded, notched, or asymmetrical on account of a gently sloping upstroke.

In 4 ballistocardiograms, the I wave failed to reach the base line, 2 showed large H waves, and 2 upward diastolic deflections that were larger than the systolic. This group of 8, classed in

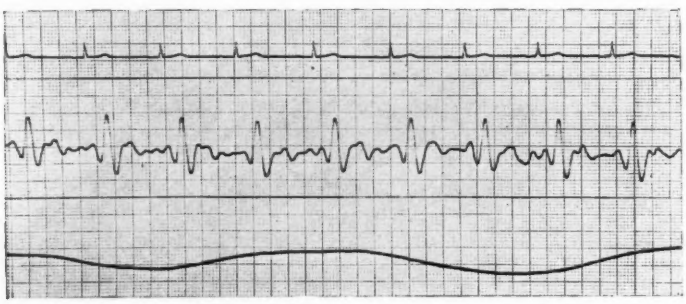

Fig. 1.—Normal ballistocardiogram obtained from a 26-year-old man. The pneumogram moves downwards during inspiration.

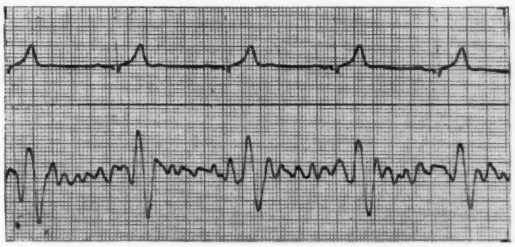

FIG. 2.—Tracing showing very deep K waves. From a 23-year-old male student.

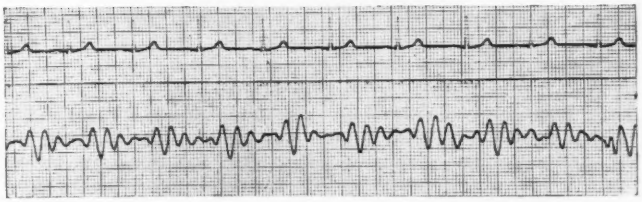

FIG. 3.—Ballistocardiogram of a 22-year-old woman student. In several complexes the diastolic waves are larger than the systolic ones.

Tables I and II as Category 2, has been divided into sub-groups (a) and (b), containing respectively a minority and a majority of abnormal waves. The former group included three with subnormal I waves, one with large H waves, and one with large diastolic waves (Fig. 3).

The subjects in Grade 1 and the two special categories did not include an unduly high percentage of patients with conditions such as diabetes, likely to be associated with cardiac disease. The proportion indulging in strenuous exercise was only slightly less than among the normals. The group with deep K waves, the form usually associated with hypertension, contained only one person with a blood pressure of over 160/90. None of these departures from normal was associated with marked axis deviation. There was a tendency for Grade 1 to include a relatively larger number of underweight patients, but about a quarter of this group was actually overweight.

The students and staff were all under 35 years of age. The patients in this age group are distributed among the various classes in a manner similar to that of students and staff (Table I). The

TABLE I

INCIDENCE OF ABNORMAL BALLISTOCARDIOGRAMS AMONG HEALTHY SUBJECTS AND PATIENTS WITH NON-CARDIAC CONDITIONS UNDER 35 YEARS

	Students and staff		Patients	
	No.	Percentage	No.	Percentage
Normal	73	73	26	62
Grade 1	4	4	6	14
Grade 2	0	0	0	0
Grade 3	0	0	1	2
Grade 4	0	0	0	0
Category 1	21	21	5	11
Category 2(a)	2	2	3	7
Cateogry 2(b)	0	0	2	4
	100		43	

TABLE II

CLASSIFICATION OF CASES ON BASIS OF AGE AND SEX

	Under 45			Over 45			All ages		
	Men	Women	Both sexes	Men	Women	Both sexes	Men	Women	Both sexes
Normal	73	46	119	5	4	9	78	50	128
Grade 1	15	1	16	7	0	7	22	1	23
Grade 2	0	0	0	2	1	3	2	1	3
Grade 3	2	0	2	1	1	2	3	1	4
Grade 4	0	0	0	1	0	1	1	0	1
Category 1.. ..	21	8	29	3	0	3	24	8	32
Category 2(a) ..	4	2	6	0	0	0	4	2	6
Category 2(b) ..	2	1	3	0	0	0	2	1	3
	117	58	175	19	6	25	136	64	200

incidence of abnormality among the patients over 45 was appreciably greater than that among patients below this age. There are rather fewer men normals than women owing to a larger number of the former in Grade 1; but the sex difference is not associated with differences in age distribution (Table II).

The constancy of the HK interval was confirmed in the case of the normal ballistocardiograms. In six Grade 1 tracings there was a variation, not constantly related to respiration, of up to 0·04 sec. and in one case in each special category there were differences of up to 0·08 sec. With greater degrees of abnormality, measurement of the HK interval became increasingly difficult, owing to irregularity of the waves. The complexes were clearly defined and identifiable in all but the Grade 4 cases and some of the expiratory waves in three Grade 3 cases. No obvious variation in the relative timing of the ballistocardiogram and electrocardiogram was seen.

The complexes, even in the normals, vary with respiration and from cycle to cycle as the cardiac and respiratory rates are unrelated, and, consequently, in each cycle systolic complexes occur in slightly different positions relative to the peaks of inspiration and expiration. This tendency is naturally greatest in the Grade 1 tracings in which the respiratory variation is great and complexes may be increasing threefold in size in the course of three or four beats. Since the shorter expiratory complexes have the same width as the inspiratory, their shapes are necessarily somewhat different and the peaks of the waves more rounded (Fig. 4). The records in the two special categories were no more variable than the normals. Single complexes that differed markedly from all others were seen not infrequently and considered to be artefacts.

With one exception, when the recorder sensitivity was standardized, the IJ waves of the normals fell in the ranges 5–22 mm. and 4–15 mm. in inspiration and expiration respectively. The IJ wave amplitudes of the subjects in Grade 1 and the two special categories lay within these limits. Among the normals in this group, who were all aged forty and under, there was a positive correlation

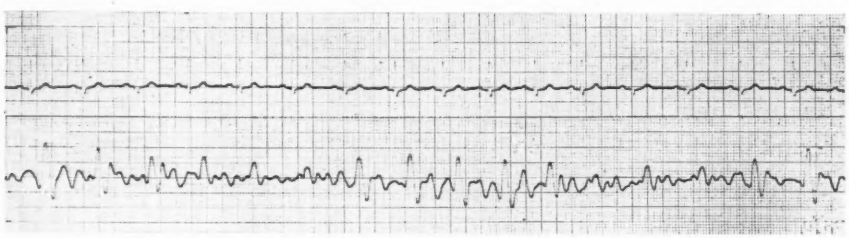

FIG. 4.—Grade 1 ballistocardiogram obtained from a 42-year-old patient admitted for treatment of a fistula-in-ano.

between mean IJ wave amplitude and height of subject ($r=0{\cdot}37$, $N=59$; $P<0{\cdot}01$), but not with weight ($r=0{\cdot}05$).

The observations were repeated on 20 members of the student-staff group at intervals ranging from one month to two years. The pattern was virtually identical in 13, and in a further 5 the systolic complexes were similar, though there were differences in the diastolic ones (Fig. 5), a variable number of L waves being larger than the J waves: these have been classified on the basis of the earlier findings. The remaining 2 showed changes in the relative depths of the I and K waves, but were normal on both occasions.

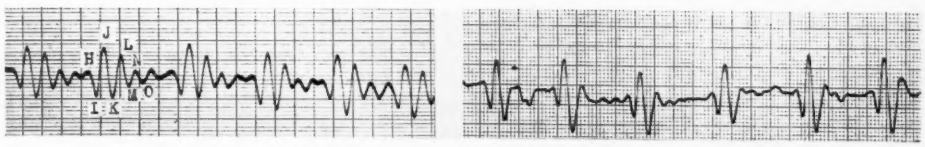

FIG. 5.—Tracings obtained from a healthy 24-year-old woman before and after an interval of twenty-two months. The right-hand tracing, which is the later one, shows some decrease in the size of the diastolic complexes, but no change in the systolic ones.

DISCUSSION

The decision to regard any observation as abnormal is necessarily based on studies of a group of apparently healthy people. The range accepted as physiological is usually one within which the vast majority, rather than the complete population, fall. A conclusion that a particular finding is pathological must always be made with this reservation.

On this basis, ballistocardiograms with continuous abnormalities, such as very large H waves or diastolic deflections, could be regarded as abnormal, being present in only 1·5 per cent of a large series of normal subjects. Similarly, Grades 2, 3, and 4, with a combined incidence of 4 per cent, could be considered pathological. It can be seen from Table II that all these types of pathological tracings were seen in only 3 per cent of subjects under 45 years of age.

Similar considerations apply to systolic waves with the form of the letter M. The " early M " associated with an abnormally large H wave, was seen only four times, and then not in a fully developed form. The " late M " produced by a reduplication of the I wave, was not seen at all. The J wave was occasionally slurred, but never notched or split. The complexes were clear cut in all but the Grade 4 and three of the Grade 3 tracings, and absence of definition is, in consequence, to be regarded as abnormal.

On the other hand, the incidence of Grade I tracings is such that they can be regarded as a normal finding, especially in view of their occurrence in the early age groups. The factors that are thought to produce the respiratory changes in the ballistocardiogram, i.e. the effect of respiration on the blood flow in the venæ cavæ and pulmonary veins, and secondarily on the output and force of contraction of the right and left ventricles, is enormously variable. The respiratory alteration in ballistocardiographic amplitude shows a continuous gradation from an amount that is hardly detectable to a more than threefold inspiratory increase, and any distinction drawn between tracings in which the change is more than twofold and those in which it is less is purely arbitrary. Jones (1952), using the low-frequency table ballistocardiograph, found this feature equally commonly in groups of patients with and without arteriosclerotic heart disease.

It seems logical, furthermore, to consider as normal the ballistocardiograms of Category 2 (a), i.e. those without marked respiratory change but with a minority of abnormal complexes, since some Grade 1 tracings show the latter feature (Fig. 4). Abrams and Edger (1953), using an electromagnetic instrument, noted the presence of I wave abnormalities in the course of a survey of 319 healthy soldiers: there were unusually large H and L waves in 1 per cent and 6 per cent respectively, the latter being considered normal by them.

Similar reasoning suggests that ballistocardiograms with deep K waves should be considered physiological. There is a continuous gradation from very shallow to very deep K waves, and their amplitude is often lessened by use of the filter. Their measurement depends on the rather arbitrary drawing of a base line which can often be placed at varying levels. Mandelbaum and Mandelbaum (1951) suggest that this type of complex can occur in tall, thin subjects, though it was by no means confined to this type in the

present series. In any case, this feature can hardly supplant the sphygmomanometer as a means of detecting hypertension, and the observation of Brown *et al.* (1952) that the K wave becomes much shallower when the blood pressure is reduced by *Veratrum viride* means that this type of complex is of no value in the detection of previous hypertension, in, say, a patient suffering from shock.

Table III shows the incidence of normality in the series when the revised criteria now being suggested are accepted. The age trend is still apparent, but the sex difference largely disappears.

TABLE III

PERCENTAGE OF NORMALS USING REVISED CRITERIA

	Over 45	Under 45	Men	Women	Total
	No.	No.	No.	No.	No.
Normal	19 (76%)	170 (97%)	128 (94·5%)	61 (94%)	189 (94·5%)
Abnormal	6 (24%)	5 (3%)	8 (6%)	3 (5·5%)	11 (5·5%)
	25	175	136	64	200

By standardizing the recording apparatus, it is possible to compare tracings with each other, and, on an empirical basis, to define for each height and age group, a range for the IJ amplitude beyond which a normal is unlikely to fall (Fig. 6). The photo-electric instrument cannot, however, be used quantitatively, e.g. to measure cardiac output, as the responses of the body to a vibrating and a momentary force are totally different, and a valid method of calibration, which must be based on the response of the body to the former, has not as yet been devised.

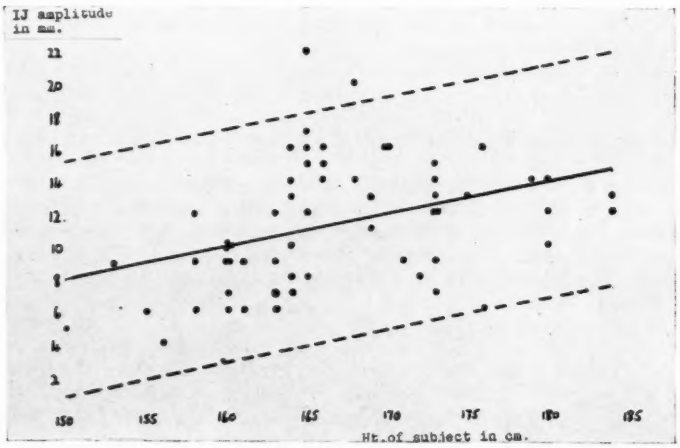

FIG. 6.—Relation of IJ amplitude to height of subject. The continuous and interrupted lines indicate the regression line and the 95 per cent confidence limits respectively.

The results were found to be constant during any one period of observation suggesting that short-term variations, such as those described by Henderson (1953), reflect real cardiovascular changes.

These conclusions suggest that ballistocardiography is of more limited use than has hitherto been suggested. Its value in large-scale surveys is limited by the need to select from the population to be studied those with the ability and willingness to co-operate. Comparing different series, as in an endeavour to assess the incidence of cardiac involvement in a particular disease, would only be possible when the distribution of abnormalities is likely to be the same among the sections of the population that can and cannot be tested. This assumption could not be made in the case of diabetes, for example. Here, the type of person

able to co-operate adequately in the test is likely to be the type of person who would approach his illness more sensibly and be better controlled, with resulting freedom from complications.

The ballistocardiograph detects weakening of the contractile force of the myocardium but not its cause. The typical patterns that have been described in a number of conditions, such as coarctation of the aorta and mitral stenosis, are of theoretical interest, but do not assist in diagnosis or assessment.

Ballistocardiography will stand or fall as an instrument of clinical practice by its value in the diagnosis and assessment of ischæmic heart disease. Previous concepts concerning its value in the subject with possible angina need modification. The series of Brown *et al.* (1950) included 5 typical and 10 atypical cases in which the diagnosis of ischæmic heart disease was maintained in the absence of evidence of cardiac abnormality: they claimed that all of these had abnormal ballistocardiograms, though in 3 of each group there were Grade 1 records. Starr (1952), who does not attach much importance to marked respiratory variation, and Scarborough *et al.* (1953), who have demonstrated it in normal subjects in the older age groups, have reported physiological tracings in patients with angina (Starr and Wood, 1943; Scarborough *et al.* 1952). The differences, however, may not be wholly attributable to differing interpretations of the significance of respiratory variation.

The single Grade 4 tracing in the present series was obtained from a subject with a considerably unfolded aorta. Dock (1954) has shown that this is often associated with pathological longitudinal but normal lateral ballistocardiograms and has suggested that change in direction of forces generated by a normal contraction of the heart is responsible. It would seem, therefore, that in a person with this feature no significance can be attached to a record that is grossly pathological. The need for a lateral tracing in these cases detracts considerably from the principal advantage of the photo-electric instrument—its simplicity.

The evidence presented suggests that a normal ballistocardiogram showing no marked respiratory variation is, in older subjects, evidence against the presence of ischæmic heart disease, and that a grossly abnormal finding in a young person with no unfolding of the aorta is to be considered pathological. The conclusions apply equally to the diagnosis of angina pectoris or coronary thrombosis, past or present. Observations need to be made on subjects with suspected ischæmic heart disease in conjunction with an assessment of the position of the heart and the state of the aorta, and the ballistocardiograms with marked respiratory variation classified separately. Long-term studies are needed in order to determine whether there is a difference in prognosis in clinically comparable cases of proven coronary artery disease with normal and abnormal ballistocardiograms.

Summary and Conclusions

Ballistocardiographic observations were made on 200 subjects without evidence of cardiovascular disease, using a photo-electric apparatus. The technical difficulties and the fallacies of quantitative deductions were pointed out. Qualitative analysis showed that 64 per cent were normal according to criteria laid down for the instrument. It was suggested that tracings in which there were a minority of abnormal complexes, with or without marked respiratory variation, and tracings normal apart from a large final systolic downstroke should be regarded as physiological. On this basis, 94·5 per cent of the tracings were normal. With the new criteria, as with the old, there was an increasing incidence of abnormality with increasing age.

The following conclusions about the practical values of ballistocardiography were reached.

(1) It can be used to assess the incidence of cardiac involvement in generalized disease processes, though problems of bias in selection arise.

(2) The effect of any agent, e.g. tobacco, on the cardiovascular system can be detected by observation of short-term changes.

(3) In a young subject with a vertical heart and no aortic unfolding, a grossly abnormal ballistocardiogram is evidence in favour of cardiac disease, and a normal tracing without respiratory variation suggests the presence of a normal heart, especially in an older person.

Dr. William Phillips suggested this work and has given continued advice and encouragement; Dr. Lewis Fanning provided statistical help; Dr. Gerald D. Davies recorded a large number of the ballistocardiograms; Miss C. Rumbelow and Miss D. Francis gave valuable technical assistance; to these and to the consultant staff of Cardiff Royal Infirmary who permitted me to study their patients I am much indebted.

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THE POSTCOMMISSUROTOMY SYNDROME

BY

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The term " postcommissurotomy syndrome " (P.C.S.) was first used by Soloff *et al.* (1953) to define an illness with a " distressingly high incidence " (43 out of 183 cases) after mitral valvotomy. The main symptoms were sternal pain with radiation to the left chest and pyrexia, the onset was mostly abrupt either days or weeks after operation and the duration varied from ten days to four weeks with frequent further relapses. The syndrome occurred either alone or in various combinations with other postoperative complications ; though the mortality was low (3 out of 43) there was an adverse influence on the outcome of the operation in more than one-third of the cases. Among the many hypotheses advanced for the pathogenesis they favoured the idea of rheumatic reactivation induced by surgical trauma. Bercu (1953), who observed the P.C.S. in 10 per cent of his patients, agreed that it may suggest rheumatic activity though trauma to the heart may be more important; the prognosis in his cases was not different from that of the uncomplicated cases. January *et al.* (1954) with a similar incidence used the term " postvalvotomy syndrome "; they did not consider the symptoms as wholly characteristic of rheumatic fever. McAllister (1953) suspected a low-grade infection of the lingula as its cause. Dressler (1954) for whom the syndrome consists of the triad, pericarditis, pleurisy, and pneumonitis, compared the P.C.S. with idiopathic recurrent pericarditis and tried to establish a rheumatic etiology for both. Verheugt *et al.* (1954) did not mention the syndrome by name, but described its signs as temporary rheumatic activity because of its successful treatment with amidopyrine and the rise in antistreptolysin titre in some of their patients. Elster *et al.* (1954), after a painstaking study of the P.C.S. in 16 patients, doubt if this is due to rheumatic fever, bacterial infection, pulmonary infarction, or direct surgical trauma; for them it represents a self-limited form of pericarditis and pleuritis induced by trauma of surgery in patients with rheumatic heart disease.

No original study of the P.C.S. has so far appeared in British publications. The comprehensive papers on mitral valvotomy by Baker *et al.* (1952), Logan and Turner (1953), Holmes *et al.* (1953) do not mention it. Wood (1954), however, devoted a short space to postoperative pericarditis with fever, observed in 10 per cent of his cases, which subsides permanently and leaves no serious consequences.

During the last four years the P.C.S. was frequently observed in our hospital. The early cases were not recognized: it was thought that too-tight pericardial suture or the incorrect *p*H of the novocaine solution injected into the pericardial sac might be responsible for the pericarditis and that the chest pain and pyrexia were due to postoperative auricular thrombosis. Some of our patients were admitted to other hospitals during relapses and diagnosed as left basal pneumonia; this shows that the syndrome is not generally known.

A study was therefore undertaken of all our patients with P.C.S. to describe their symptoms and to find out more about the origin of their illness. Admittedly a rheumatic flare-up could be expected after valvotomy; the finding of Aschoff nodes in 20–40 per cent of the excised auricular appendages by others and the positive laboratory tests for rheumatic activity and for

adrenocortical hypofunction following operation (Cordeiro *et al.*, 1954), suggested that valvotomy was frequently performed during rheumatic activity. Nevertheless a rheumatic hypothesis for P.S.C. sounded unconvincing because of the rare incidence—2 per cent in our series—of overt rheumatic recurrences after valvotomy. More attention has therefore been devoted in this investigation to the local postoperative conditions which may constitute the possible cause of the P.C.S.

Material and Investigation

Out of 100 patients who had mitral valvotomy, 22 were selected for study; in these either the early or late postoperative period was complicated by a prolonged illness with pyrexia, pericarditis, left pleural effusion and tendency to relapse. There were 5 men and 17 women. The ages ranged from 26 to 52 with an average age of 37. Altogether 26 episodes were observed in these patients; 19 patients were seen during their illnesses while in 3 data from other hospitals were available. Special investigations included chest films at least twice weekly; frequent electrocardiographic recordings in many; culture and microscopy of the pleural effusion, white cell counts, and E.S.R. in some.

The cases fell into two groups.

Group I comprised 14 patients with 16 episodes. Here the illness followed closely upon the operation (11 cases) or started after a time lag of 5–11 days after operation (3 cases). The average duration of the illness as calculated in days of pyrexia was 17 days with a range of 8–34 days (Fig. 1A). Two patients (Cases 2 and 3) had relapses 2 and $2^1/_2$ months later lasting 21 days and 2 months respectively (Fig. 2).

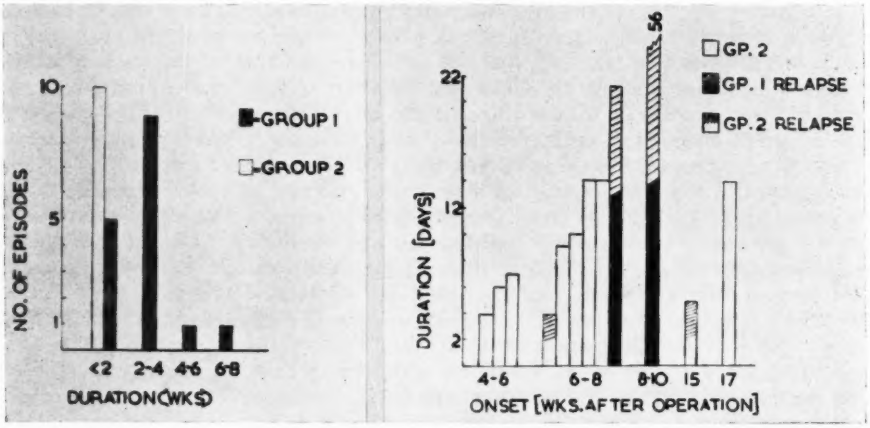

FIG. 1.—(A) Duration of pyrexia in 16 episodes in 14 patients of Group I (black columns) and in 10 episodes in 8 patients of Group II (white column). (B) Time of onset and duration of pyrexia in 8 patients of Group II with two relapses (shaded white columns) and in 2 patients of Group I (shaded black columns) who relapsed. Each column represents one episode.

Group II comprised 8 patients with 10 episodes. Here the patients left hospital in less than 3 weeks and the illness appeared at intervals after operation varying between 4 weeks and 4 months (Fig. 1B). The period of illness was much shorter than in Group 1 (Fig. 1A); it ranged between 4 and 14 days with an average duration of 9 days. Two patients (Cases 7 and 12) had relapses after 3 and 7 weeks.

Since the syndrome in Group I followed so closely upon the postoperative period, the nature and duration of the normal postoperative sequelæ in 35 patients with uncomplicated course were also studied.

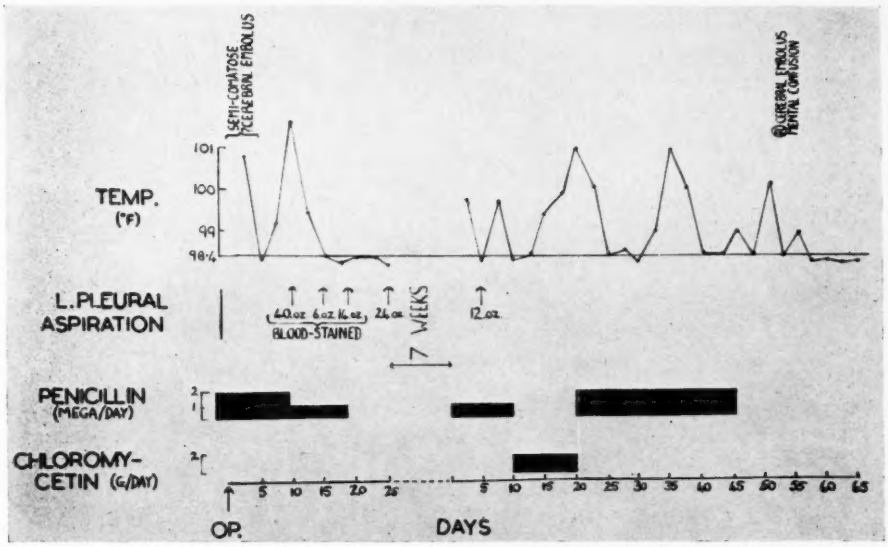

FIG. 2.—Case 3, showing relapse after 7 weeks.

THE NORMAL POSTOPERATIVE SEQUELÆ

After the first few days the incisional pain subsides; at the end of the first week or even earlier the patient sits out; he becomes ambulatory after 10–14 days and after three weeks is ready for convalescence. There may be some postoperative pyrexia which seldom lasts longer than four days. The effusion from the left chest drains away during the first 24 to 48 hours after which the intercostal drainage tube is removed. In most of the patients some effusion reforms, but aspiration is rarely necessary, and at the end of the second week the chest film shows only pleural thickening but no effusion in 75 per cent of the patients. In the remainder the effusion absorbs during convalescence. In the few isolated instances where aspiration was performed after the first week the liquid was usually straw-coloured. Though the patient rarely complained of severe central chest pain, a transitory pericardial rub was heard in 65 per cent of cases during the first week. Electrocardiographic evidence of pericarditis during this period was found in 4 out of 10 patients where early electrocardiograms were recorded (Fig. 3). A left pleural rub was heard frequently. In two instances a right pleural rub was heard without the patient complaining of pain and without signs suggesting pulmonary infarction. Polymorphonuclear leucocytosis and raised E.S.R. were frequently present and persisted beyond the febrile period.

THE POSTCOMMISSUROTOMY SYNDROME (P.C.S.)

The symptoms were similar to the normal postoperative sequelæ; they were identical in Group I and Group II though they were more severe and of longer duration in Group I, particularly during relapses (Cases 2 and 3).

Pyrexia was moderate and continuous; it varied from 99°–100° F. with occasional spikes to 101°–102° F. Its duration was variable (Fig. 1A and B); when the temperature fell to normal it rarely remained so but continued around 99° F. for some days. Alternatively the fever remitted for a day or two, then started again (Fig. 2). Rigors were not seen except in one patient where the

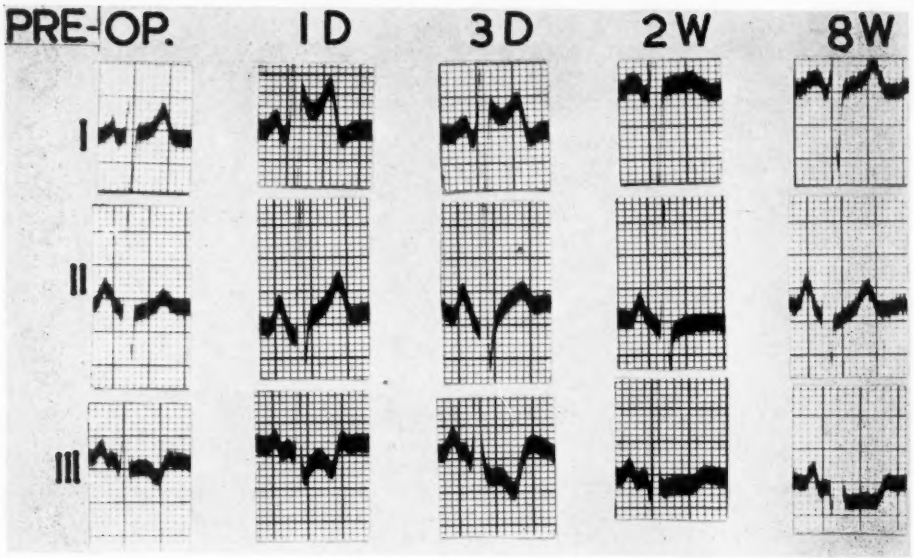

FIG. 3.—Uncomplicated mitral valvotomy. Typical changes of pericarditis in the early postoperative period, regressing after 2 weeks, disappearing after 8 weeks.

TABLE I

SIGN OF PERICARDITIS IN THE POSTCOMMISSUROTOMY SYNDROME

Case No.	Rub	Pain	EC.	X-rays
1	No	No	Yes	Yes
2	No	Severe	Probable	No
3	Yes	Severe	Probable	No
4	Yes	Yes	Yes	No
6	Yes (post-op.)	No	Yes (relapse)	No
8	No	No	Probable	No
9	No	No	Yes	No
11	Yes	Yes	No	No
12	No	No	Yes	No
13	Yes	No	Yes	No
14	Yes	No	Yes	Yes
15	Yes	No	Yes	No
16	Yes	Severe	Yes	No
17	Yes	No	Yes	No
18	Yes	No	—	No
19	Yes	No	Yes	No
22	No	Yes	Yes	No

effusion became infected. Persistent pyrexia as a symptom was important for it distinguished P.C.S. from the normal postoperative sequelæ.

Pericarditis. The signs and symptoms of pericarditis are pericardial rub, central chest pain, electrocardiographic S–T and T wave changes, and sudden increase in size of the heart shadow in the chest film. These signs were present alone or in various combinations; the most frequent association was that of pericardial rub with electrocardiographic abnormalities. A pericardial rub was more often observed than pain (Table I), and in fact the two were often dissociated. In

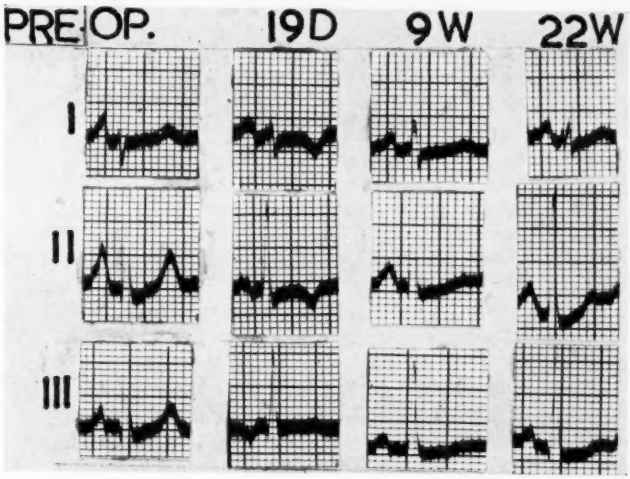

FIG. 4.—Case 1. Typical changes of pericarditis at 19 days regressing after 9 weeks; record still abnormal at 22 weeks.

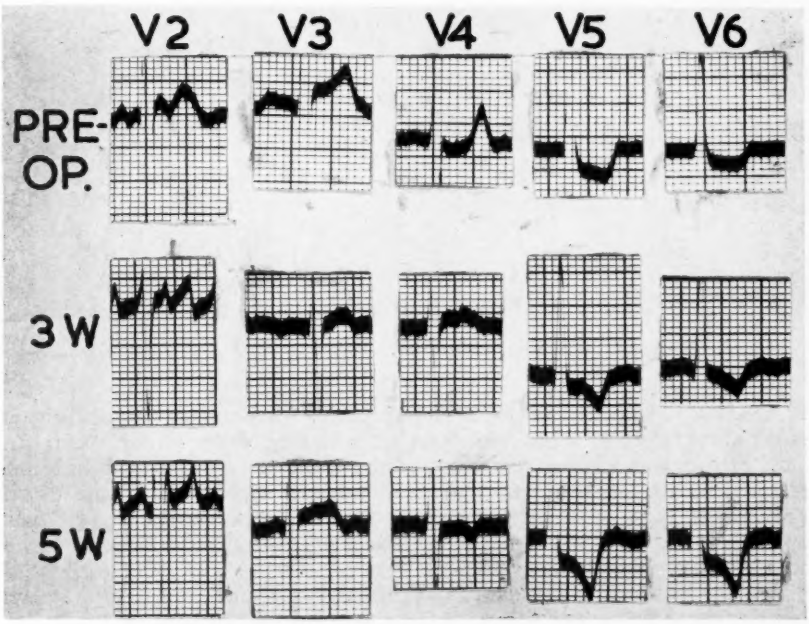

FIG. 5.—Case 4. Combined digitalis and pericarditis changes producing S–T and T pattern resembling ventricular strain in V5–V6. Preoperative digitalis changes affect V5–V6 only while postoperative pericarditis changes extend as far as V3.

contrast to the fleeting postoperative rub in the uncomplicated cases it persisted for more than four days in most of those patients. In Cases 15 and 17 it changed site, shifting from the lower sternal region to the base of the heart. In Case 14 it was still present two months later.

Electrocardiographic changes, though often obscured by digitalis effect, were recognized in 15 out of 19 cases. While the patterns of pericarditis alone were prominent in the limb leads (Fig. 4), when combined with digitalis effect, the chest leads were more helpful (Fig. 5). Here again, in contrast with the uncomplicated cases (Fig. 3) the changes persisted for many weeks (Fig. 4) or appeared during convalescence (Fig. 8).

Central chest pain was not a prominent feature in our series. It was present in 6 patients and was severe in 3 only, being the reason for readmission in 2 (Cases 2 and 3). It had the usual character of pericardio-pleural pain; it was stabbing, made worse by coughing, deep breathing, or any movement, and when severe was responsible for a fast and shallow respiration easily confused with the dyspnœa of congestive heart failure. Pain over the left base of moderate intensity was present in 3 instances and was erroneously attributed to the wound pain of the thoracotomy. Occasional pain in the left shoulder tip suggested diaphragmatic involvement. Pain on the right side of the chest was not observed.

The radiological sign of pericarditis—the sudden increase in size of the heart shadow—was observed in two instances only (Fig. 6). The presence of left basal effusion obscuring the left cardiac border made it impossible to estimate the heart size in the others. Pericardial aspiration did not yield any fluid in the two patients in whom it was attempted.

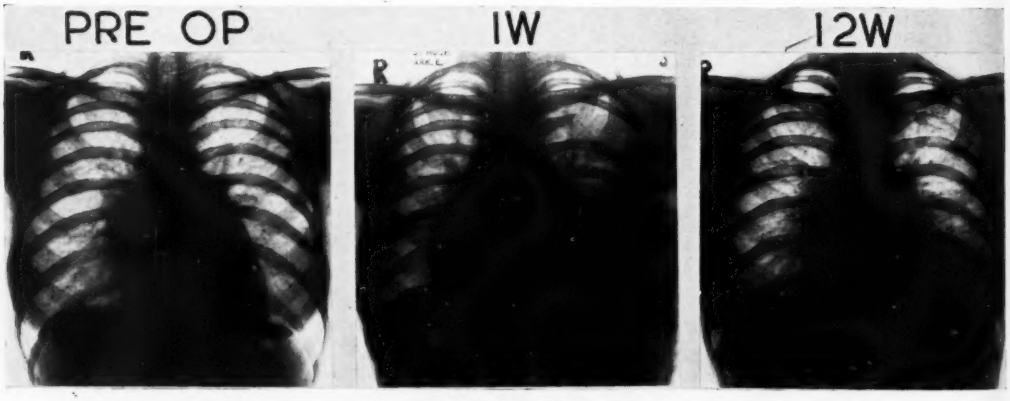

FIG. 6.—Case 1. Sudden increase of heart shadow at 7 days due to pericarditis.

Pleural Effusion. The persistence of left basal effusion for weeks or months or its recurrence after apparent absorption constitutes, with pyrexia, the leading feature of the P.C.S. In the chest film the fluid reaches its maximum, the upper border of the posterior aspect of the sixth to eighth rib in the mid-clavicular line, between the fourth and seventeenth postoperative day and when aspirated reforms quickly. Following absorption of the fluid pleural thickening remains in the left costophrenic angle where small amounts of fluid may again collect in association with pyrexia and further relapse (Fig. 7 and 8).

Paralysis of the left dome of the diaphragm through accidental damage to the phrenic nerve during operation may have been an additional factor in Cases 10 and 13 retarding recovery.

In 4 patients (Cases 2, 14, 15, and 19) loculation of the effusion occurred between the pericardium and pleura in the anterior part of the chest (Fig. 9). One of these (Case 2) was the most

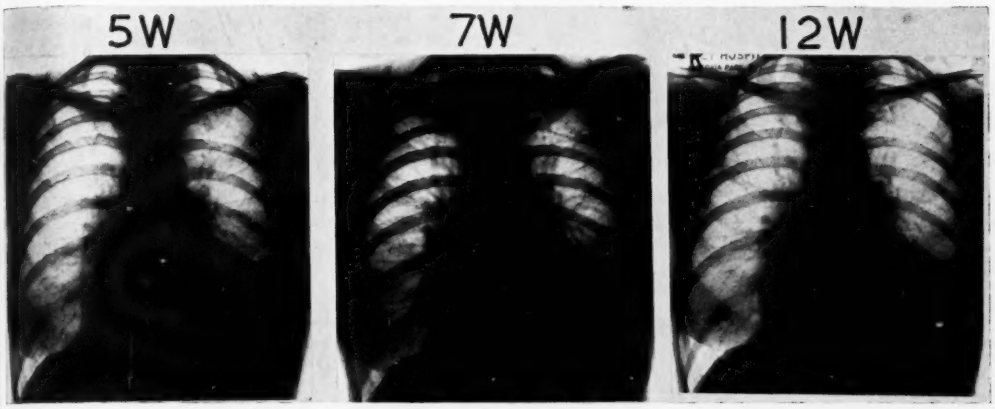

FIG. 7.—Case 3. Left pleural effusion still present at 5 weeks at discharge; partial clearance during convalescence; reappearance at 12 weeks during relapse.

TABLE II

LEFT PLEURAL EFFUSION IN THE POSTCOMMISSUROTOMY SYNDROME

Case No.	Appearance	Cultures	Aspiration	
			Days after operation	Amount (oz.)
2	Pure blood	Sterile	Rep. 6–25	Few oz.*
3	Bloodstained	Sterile	10, 14, 19	40, 6, 14
2nd admission	Straw-coloured	Sterile	75	12
8	Bloodstained	Sterile	8	6
9	Bloodstained	Sterile	6	Few oz.
10	Bloodstained	Sterile	8	24
11	Bloodstained	Sterile	14	Few oz.
13	Bloodstained	Sterile	8	6
15	Bloodstained	Sterile	5	6
	Purulent	Haem. staph. aureus	17	Few oz.*
18	Bloodstained	Sterile	22	40
19	Bloodstained	Sterile	7	Few oz.*
22	Straw-coloured	Sterile	60	13

* Aspirated from anterior loculi.

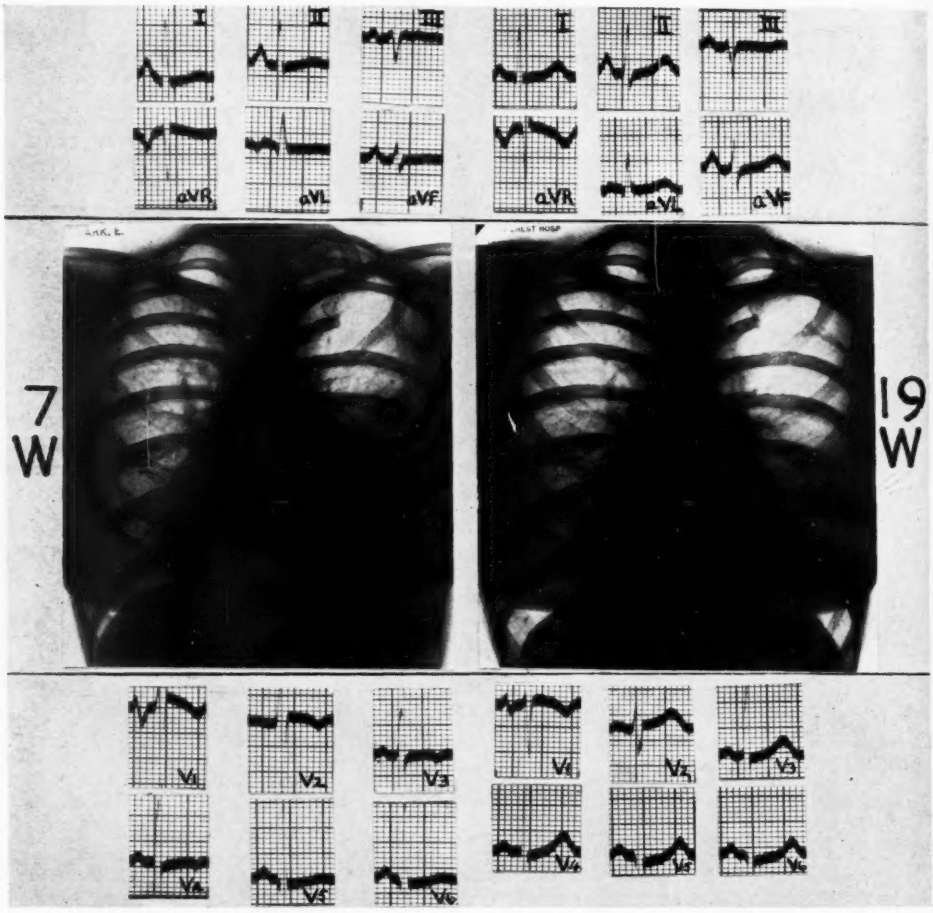

FIG. 8.—Case 12. Normal postoperative course. Appearance of left pleural effusion at 7 weeks, with changes of pericarditis in the electrocardiogram. Complete radiological clearance and normal record at 19 weeks.

severe of our cases; the P.C.S. lasted almost 3 months with a few weeks intermission between two bouts of illness. Cases 14 and 19 were of moderate severity. The fourth (Case 15) recovered in 19 days, 4 days after the pocket, which was infected, was emptied.

Laboratory data of the effusion were available in 11 patients (Table II). The fluid was blood-stained in 10 where the aspiration was performed between the fifth and twenty-second postoperative day. It was straw coloured in Case 22, two months after the operation, and purulent in Case 15 on the seventeenth day, when culture revealed the presence of hæmolytic *Staphylococcus aureus*. In the others the cultures were sterile. The cellular composition suggested inflammatory exudate with a prevalence of neutrophils.

The Lungs. Left basal effusion obliterates the underlying lung fields in the chest film. When the fluid absorbs crepitations may be heard but at this stage pleural thickening obscures the lung

changes. It is likely that under extensive effusions pulmonary basal consolidation develops. This was proved in our only direct observation (Case 4) in a patient who 7 months after mitral valvotomy followed by P.C.S. underwent a second thoracotomy for aortic stenosis: there were dense pleural and pleuro-pericardial adhesions over the left base and the lower third of the left lung showed carnification.

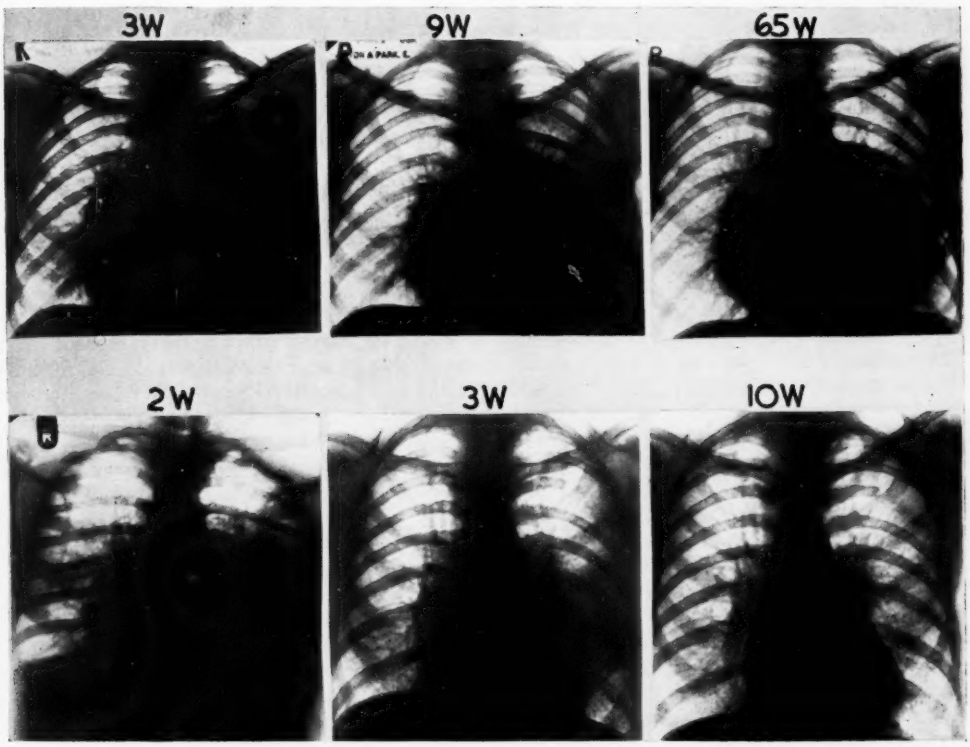

FIG. 9.—(A) Case 2. Hæmothorax after sling operation for mitral incompetence with anterior loculus formation at 9 weeks. Clearance with retraction of left chest. (B) Case 19. Anterior loculus formation after mitral valvotomy at 2 weeks; after aspiration at 3 weeks; complete clearance at 10 weeks.

The hæmatological findings were too variable to be of diagnostic help. The leucocyte count at the height of the syndrome varied between 12,000 and 40,000 with 73–82 per cent neutrophils and bore no relation to the severity of the syndrome. The E.S.R. in the postoperative cases was unreliable; in the relapsing cases it was moderately raised to 30–40 mm.

DIAGNOSIS

The P.C.S. has some features in common with rheumatic pericarditis and has been attributed to it. The pericardial involvement, the persistent pyrexia, the tendency to relapses, the increased E.S.R. are present in both conditions. However, there are many more dissimilarities.

	Rheumatic Fever	P.C.S.
Preceding streptococcal infection	frequent	never
Arthritis	present	absent
Carditis	present	absent
Constitutional upset	great	slight
Outcome	possibly fatal	good prognosis
Salicylate effect	invariable	absent
Aschoff bodies	probable	not found

Latent streptococcal infection could be ruled out since all patients had routine penicillin treatment after operation.

The absence of articular involvement was particularly striking. Rheumatic relapses, though rare, may occur after valvotomy and joint pains in them are the rule (illustrative case M.S.). Rheumatic recurrence may also be associated with the P.C.S. in rare instances (illustrative case E.P.) and in these salicylate effect may be manifest; but joint pains and articular swellings are not part of the P.C.S.

The pericarditis of rheumatic fever is a partial manifestation of generalized cardiac involvement. The pericarditis of the P.C.S. is a local process that leaves the valves and the myocardium unaffected. Prolongation of the Q–T interval and delay in atrio-ventricular conduction were not observed in the electrocardiogram. Out of 13 patients of our series with sinus ryhthm before operation 5 developed auricular fibrillation after it and of these sinus rhythm could be restored in two. The incidence of 23 per cent in whom auricular fibrillation became established is therefore similar to that in patients without P.C.S. Postoperative congestive heart failure was observed in 3 patients and this incidence (14%) is actually the same as in the group without P.C.S. The effect of digitalis and mercurial diuretics was similar in those with and without P.C.S. and when fever abated, often spontaneous diuresis set in. No further valves became affected during the illness.

The absence of Aschoff bodies in the auricular appendages of our series is the least impressive argument against rheumatic activity. Opinion among pathologists is so divided as to what should be regarded as an " active " Aschoff body (Enticknap, 1953; McKeown, 1953) that their presence or absence is more a subjective impression than an objective finding (Hinson, 1955). In our hospital, where strict criteria have been applied such a finding was exceptional (2%).

Pulmonary infarction also causes severe chest pain with basal effusion and may be confused with the P.C.S. Its sudden onset with shock, blood-stained sputum, signs of thrombophlebitis in the leg veins, and the electrocardiographic patterns of acute right ventricular strain are the differentiating features. The diagnosis is easy if radiological changes develop on the right side; but if these are on the left side and are obscured by the postoperative effusion they may be impossible to detect. If the diagnosis is doubtful, anticoagulant treatment may be given; this is followed by rapid improvement if imarction is the cause, but it leaves the P.C.S. unaffected. Both conditions may of course coexist.

Cerebral embolus complicated P.C.S. in Case 3. We believe that the " psychosis " described as part of the syndrome by Soloff *et al.* (1953) may be due to this.

Prognosis. This is remarkably good. The patients do not look unduly ill and however long the illness lasts they eventually recover. There was a marked contrast in many of our patients between the extensive objective signs of pericarditis, pleural effusion, and fever, and the slight constitutional upset. They lost little weight during the illness and the appetite remained fair.

Treatment. All available antibiotics were tried in the early cases, before we knew much of the syndrome, in the hope of influencing the basal pulmonary consolidation which we thought might be the cause of the fever. Like others we have not seen any conclusive results. Neither were we impressed with the effect of aspirin or salicylates except in the patient with joint pains. In an illness with such a variable course and duration any effects attributed to treatment have to be weighed critically. If the relapse is short any treatment may be regarded as effective; in fact

patients with short relapses treated in other hospitals were considered to have had good responses to penicillin treatment.

Discussion

The P.C.S. appears as the accentuation, prolongation, and recurrence of the normal postoperative sequelæ. In view of the slight systemic upset it causes and its relative benignity, local rather than general causes have to be sought to explain its persistence and the subsequent relapses.

The surgical technique was the same in all our cases. After amputation of the auricular appendage and closing of the auricular wound the pericardium was loosely stitched with interrupted sutures leaving a free communication between pericardial cavity and left pleural space. Thus the effusion draining through the intercostal tube is derived partly from the pericardial sac. Under normal conditions it is hæmorrhagic during the first few days, but becomes serous and straw-coloured after the first week if it still persists. In the P.C.S. the effusion was blood-stained in all the 10 patients in whom it was aspirated after the fifth day. Prolonged oozing from the auricular wound into the pleuro-pericardial space may be an important cause since blood in the serous cavities is regarded as a powerful irritant (Holmes Sellors, 1954). It may set up a foreign body reaction in the pericardium, with which Wood (1954) compares the syndrome.

Case 2, who developed a frank hæmothorax after a sling operation for mitral incompetence had the longest illness of all and recovered eventually with a retraction of the left chest.

It may be possible that rheumatic subjects show an increased irritability of their serous membranes to extravasated blood. Massell *et al.* (1937) were able to produce subcutaneous nodules, similar, if not identical in histological structure to rheumatic nodules (Mote *et al.*, 1937) by subcutaneous injection of blood in 90 and 50 per cent of their patients with clinical and subclinical rheumatic fever respectively: only in 3 per cent of normal controls did nodules develop.

Another important local factor that may coexist is the pocketing of the effusion; though this was observed in only 4 cases, the aspiration of the pockets in 2 resulted in immediate improvement and rapid recovery. These pockets were anteriorly situated; the insertion of the drainage tube in the posterior axillary line might be responsible for their site. The dense adhesions around them made their detection difficult.

The local factors that we consider as the cause of the P.C.S. have hitherto escaped attention. A common opinion seems to be that the P.C.S. is due to rheumatic activity. Clearly a confusion exists in earlier reports between P.C.S. and genuine recurrences of rheumatic fever after valvotomy as described by Soulié *et al.* (1954) which we believe are two distinct entities that can be differentiated. The clinical condition that most resembles P.C.S. is idiopathic recurrent pericarditis (Dressler, 1954). Patient H.S., now aged 43, is our only case of this kind under observation. From 1936 till 1953 he had eight relapses lasting from one to three weeks, with pericardial rub, mild pyrexia, minimal rise of E.S.R. and slight electrocardiographic changes. No rheumatic or tuberculous ætiology could be established in this otherwise very fit man.

The strongest argument advanced in favour of rheumatic activity is the absence of P.C.S. after operation in congenital heart disease. Our material of congenital cases is too small to be used for comparative study, but in one case clinical and electrocardiographic signs of pericarditis with associated rapid increase in size of the cardiac silhouette followed Blalock anastomosis. The electrocardiograms published by Brock and Campbell (1950) after infundibular resection for infundibular stenosis are similar to our Fig. 3 and may be interpreted as due to pericarditis. The only operation for congenital heart disease that is similar in surgical trauma to mitral valvotomy is that for auricular septal defect and here an illness similar to that of the P.C.S. has been observed (Likoff, 1954).

Until more reliable laboratory tests for rheumatic activity are forthcoming the P.C.S. should be considered as due to local trauma, with postoperative hæmorrhage and loculus formation as the main causative factors. Though it should be recognized as a clinical entity, its importance should not be overrated; it may be prolonged, but spontaneous recovery is the rule and it has no

adverse influence on the outcome of the operation. The additional discomfort it causes in 22 per cent of the patients after mitral valvotomy is a small price to pay for the lasting benefit conferred by the operation.

Summary

The postcomissurotomy syndrome (P.C.S.), an illness characterized by pyrexia, pericarditis, left pleural effusion, and tendency to relapses, was observed in 22 out of 100 patients who had mitral valvotomy. It followed closely upon the operation in 14 patients (Group I) or appeared after a time lag of four weeks to four months following operation in 8 patients who had a normal post-operative course (Group II). Two patients in each group had further relapses.

Pyrexia was moderate and continuous and lasted from 8 to 34 days in Group I and from 4 to 14 days in Group II.

Pericarditis was mostly revealed by the electrocardiogram and the presence of a pericardial rub. Pain was infrequent and radiological signs were exceptional.

Left pleural effusion persisted for weeks or months and recurred after apparent absorption. It became loculated in 4 patients; emptying of the pockets in 2 led to rapid recovery. The effusion was blood-stained in 10 out of 11 patients, when aspirated between the fifth and twenty-second postoperative day. The cultures with one exception were sterile.

Relapses, with similar symptoms and duration, occurred 3–10 weeks after the first bout of illness.

Comparative study in uncomplicated cases showed that a few days of pyrexia, left pleural effusion, which becomes serous after the first week and absorbs within a fortnight, and transitory signs of pericarditis are part of the normal postoperative course. The P.C.S. thus appears as the accentuation, persistence, and recurrence of the normal postoperative sequelæ. It is caused by postoperative oozing from the auricular wound, as shown by the blood-stained effusion, responsible for a recurrent pleuro-pericarditis. Loculation of the effusion and left basal lung consolidation may constitute additional factors. Though the P.C.S. has some features in common with rheumatic pericarditis and has been attributed to it, it should be distinguished from the latter by the absence of preceding streptococcal infection, the absence of arthritis, of carditis, of a positive salicylate effect, features that were present in the few instances of overt postoperative rheumatic recurrence. There is no available specific treatment. The disease, however prolonged, causes little systemic upset, has a good prognosis and has no adverse influence on the outcome of the operation.

Illustrative Cases

Postcommissurotomy syndrome. A woman, aged 50 years, had been breathless on effort for two years, increasingly so for six months, with orthopnœa for six weeks. On examination she was dyspnœic on slight exertion. She had mitral stenosis with slight incompetence, and auricular fibrillation but no peripheral signs of congestive heart failure. Radioscopy showed mitral shaped heart with some enlargement. At operation (12/2/52) tight stenosis was found and a good split was performed.

Postoperative course. The patient was semi-comatose for three days with transient weakness of the left side of the body (? cerebral embolus). There was persistent pyrexia from the first to fourteenth post-operative day with no response to penicillin (Fig. 2). The electrocardiogram showed evidence of pericarditis. Blood-stained effusion was aspirated from the left pleural cavity on the tenth day (40 oz.), fourteenth day (6 oz.) and nineteenth day (14 oz.). The effusion became straw coloured when aspirated on the twenty-fifth day (26 oz). There was no congestive heart failure and there were no joint pains at any stage.

Progress at home was satisfactory for the next seven weeks when she developed pyrexia and complained of severe pain across the front of the chest. When re-admitted to hospital left pleural effusion was present (Fig. 7). Aspiration yielded 12 oz. of straw-coloured fluid; the electrocardiogram showed persistent abnormalities of pericarditis. Irregular fever continued for eight weeks with no response to penicillin or chloramphenicol. There was no congestive heart failure and she never complained of joint pains. In the eighth week she became mentally confused and developed some weakness of the left arm and leg with complete recovery in two days (cerebral embolus). Subsequent progress has been good and she has experienced a fair increase of effort tolerance maintained till the present time.

Postcommissurotomy Syndrome with Rheumatic Recurrence. A woman, aged 46 years, had rheumatic fever when aged 14 with a recent recurrence at the age of 42. For 10 years she has been short of breath on effort and was admitted to hospital on three occasions for treatment of congestive heart failure. Recently orthopnœa set in and she had hæmoptysis on one occasion. On examination she was dyspnœic on slight exertion. There were signs of mitral stenosis with pulmonary hypertension, a good opening snap and auricular fibrillation, but no peripheral signs of congestive heart failure. Radioscopy showed generalized cardiac enlargement with large left auricle and right ventricle and pulmonary congestion. At operation (18/2/52) the mitral valve was found to be tightly stenosed and calcified; a good split was performed but slight incompetence was produced.

Postoperative course. The patient was febrile from the fourth to twelfth postoperative day with no response to penicillin or chloramphenicol. Thereafter she was apyrexial for three months, but during this period she experienced no subjective improvement. She had to be admitted as an emergency three-and-a-half months after operation on account of severe præcordial pain and fever. She had an extensive pericardial rub and one week later she developed generalized joint pains. There was a leucocytosis of 34,000 and she developed congestive heart failure. On treatment with salicylates and mercurial diuretics she improved and she was discharged from hospital after two months. Her subsequent course was complicated by recurrent congestive heart failure and severe dyspnœa. She died in congestive failure 18 months after operation.

Rheumatic Recurrence Two Years after Valvotomy. A woman, aged 27 years, had chorea from 8 to 10 years of age but no rheumatic fever. She had been breathless on effort for 18 months; recently she had repeated large hæmoptyses and two attacks of pulmonary œdema. Her effort tolerance has been much restricted since, on account of orthopnœa. On examination she was in sinus rhythm with no peripheral signs of congestive heart failure. There was mitral stenosis with considerable pulmonary engorgement on radioscopy, but little cardiac enlargement. At operation (1/8/50) severe stenosis was found and a good split performed.

Postoperative course. Recovery was uneventful with great improvement and she became able to lead an unrestricted life for two years. In January 1953 she developed rheumatic fever and was treated at another hospital for one month, with two further months in bed at home. Thereafter she remained well until October, 1954, when orthopnœa again became evident and an aortic diastolic murmur was detected. In November, 1954, auricular fibrillation set in; it could not be converted to sinus rhythm by quinidine. In spite of control of the ventricular rate with digitalis, the effort tolerance deteriorated and orthopnœa increased. Cardiac catheterization showed P.C.V. mean pressure 35 mm. Hg and P.A. mean pressure 55 mm. Hg. Re-stenosis was diagnosed; this was confirmed at a second valvotomy (12/4/55), when a good split was performed. Great subjective improvement followed and this is still maintained at the present time.

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THE SIGNIFICANCE OF ADVENTITIAL INFILTRATIONS IN CORONARY ATHEROSCLEROSIS

BY

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There are a large number of deaths from coronary disease in which a necropsy examination generally gives less evidence of the exact cause of death than the clinical findings. In the absence of fatal structural lesions, acute coronary deaths have been attributed to disturbances of function such as inhibition, arrhythmias, and coronary spasm; but the problem has been one of debate rather than observation. Albutt rejected the spasm theory in no uncertain terms, saying " The truth is, spasm of the coronary arteries is a nosologist's conceit to explain puzzles of his own making."

The object of this investigation was to attempt to establish some correlation between the histological features of the coronary arteries and the mode of dying. Attention was directed to the changes in the adventitia and in particular to the frequent occurrence therein of discrete foci of inflammatory cells. The incidence of these lesions is analysed, the appearances described, and their significance discussed.

METHOD

The observations presented here are based on the histological examination of the coronary arteries obtained from 160 necropsies. Of these, 101 were from cases dying of coronary artery disease, and 59 from cases in which death was due to some other cause. These are hereafter referred to as " coronary cases " and " non-coronary cases."

The coronary cases were classified independently of the histological findings into three groups. Group I: sudden deaths with coronary atherosclerosis, but no macroscopic evidence of thrombosis or myocardial infarction or fibrosis. Group II: sudden deaths with old infarction or myocardial fibrosis. Group III: deaths due to recent myocardial infarctions.

To some extent this may be considered as a classification of the immediate cause of death. In Group I the immediate cause of death was a functional disturbance rather than an anatomical lesion. In Group II, anatomical lesions were present and may be implicated, although, as these were old lesions, their presence may not always have had direct bearing on the mode of death. In Group III the anatomical lesions were more recent and may reasonably be considered to have had a more direct relationship to the immediate cause of death, although a terminal functional disturbance could not be excluded.

In all cases the histological appearances were graded according both to the degree of atheroma and to the degree of focal adventitial infiltration.

The degree of atheroma was arbitrarily assessed according to the degree of the narrowing of the lumen, and divided into four grades. Grade O: no atheroma. Grade I: slight atheroma with insignificant narrowing of the lumen. Grade II: moderate narrowing of the lumen. Grade III: complete or almost complete occlusion.

The adventitial changes were classified into four grades. Grade O: no adventitial infiltration (negative). Grade I: a scanty incidence of small or early focal infiltrations. Grade II: a small or moderate number of well-formed foci. Grade III: many well-formed foci. Grades I, II, and III are collectively referred to as " positive."

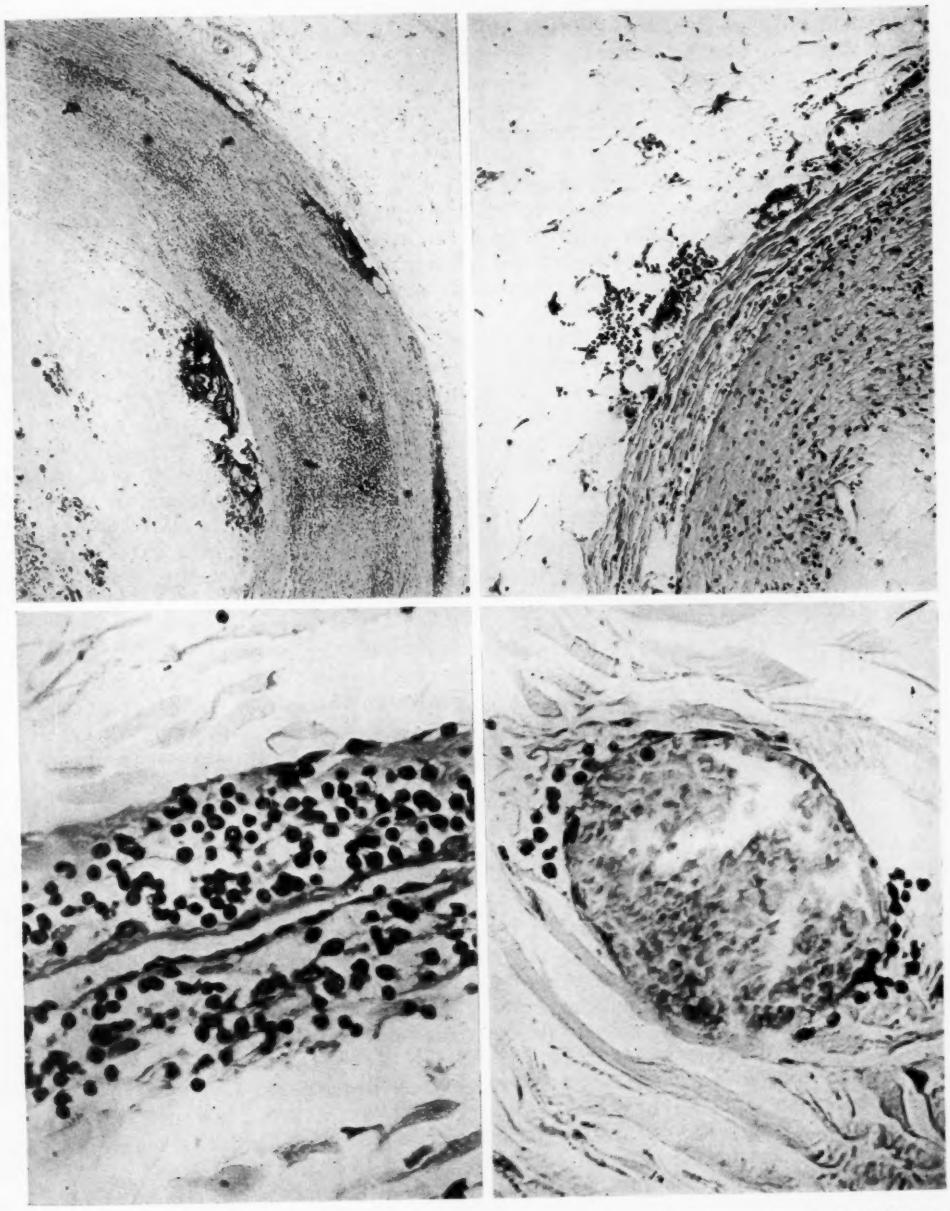

FIG. 1.—(A) Low-power view of a segment of an atheromatous coronary artery showing three foci of infiltration in the outer zone of the adventitia. (B) A small irregular focus of cellular infiltration at the periphery of the adventitia abutting directly onto the epicardial fat. (C) High-power view of an adventitial focus surrounding a small capillary in longitudinal section. The uniform cell type is demonstrated. (D) An early perivascular lesion of bipolar type in association with a dilated adventitial capilliary.

The Adventitial Lesions

Adventitial changes receive scanty recognition in studies of coronary atherosclerosis. This is probably due to the fact that atheroma is primarily a disease of the inner coats of the artery, and studies directed to the pathogenesis of the disease tend to focus on the intimal and medial lesions. The present series of observations is in no way concerned with the ætiology of the atheromatous disease, but attempts to throw some light on the mechanism by which such lesions may cause sudden death.

Gould (1953) mentions the occurrence of adventitial infiltrations in coronary atheroma and passing reference is made to it in cases reported by Miller and Woods (1943) and Zachs (1943). The presence of adventitial infiltrations in acute fatal coronary occlusions in young soldiers has been noted by Reich (1948), Saphir and Gore (1950), French and Dock (1944) and Yater *et al.* (1948). Saphir and Gore suggested that they may represent a primary inflammatory process to which the intimal changes are secondary, producing, in later stages, an appearance that cannot be distinguished from, or is identical with arteriosclerosis. Horn and Finklestein (1940), in a study of 100 fatal cases of coronary occlusion, recognized adventitial infiltration as a frequent accompaniment of coronary arteriosclerosis and drew attention to the possibility of confusion with syphilitic disease. Hausemann (1949) regarded this cellular infiltration, which he found in nearly all cases of coronary atherosclerosis, as the expression of a secondary reparative process.

The adventitial lesions consist of discrete foci of small round cells which appear to be identical with lymphocytes (Fig. 1). The distribution is essentially perivascular, forming collars around the vasa vasorum of the large coronary arteries. Early lesions can be identified as small groups of cells immediately adjacent to the vasa, and the typical established foci are of elliptical or crescentic shape when seen in transverse section. In some cases the foci are confluent producing an encircling zone around the coronary artery. These foci were not observed in association with smaller intramuscular vessels in the myocardium.

The cellular exudate or infiltrate appears to be of a pure or unicellular type (Fig. 1C), in contrast to the pleomorphic nature of the infiltrations sometimes seen in the medial layer in an area of degenerate atheroma, where plasma cells, granulocytes, macrophages, and even fibroblasts may be present. It also bears no similarity to the diffuse infiltrations as seen in polyarteritis nodosa, where eosinophil granulocytes form a prominent part of the picture, or to the histological appearances of mycotic arteritis.

In a small proportion of lesions the foci of infiltration were related to a nerve rather than to a vessel. In such cases the primary relationship is probably with the perineural lymphatics as the infiltration was entirely outside the nerve sheaths and there was no evidence of pathological change in the nerve fibres themselves.

The site of the foci appears to be determined by the position of the vasa vasorum. If these are situated in the inner portion of the adventitia, the foci may appear to be surrounded by connective tissue, and if this shows excessive fibrosis the resulting appearance may be suggestive of fibrosis directly associated with the focus. Further observation, however, shows no relationship between the degree of adventitial fibrosis and the existence or distribution of these foci.

When the vasa vasorum are situated in the outer zone of the adventitia, the foci present tend to be superficial and abut directly onto normal epicardial fat. In some instances lesions could be seen at some distance from the artery, as isolated groups of small round cells lying in the adipose tissue, in association with a capillary blood vessel, with no suggestion of cell damage or fibrosis.

Incidence of Adventitial Foci. Details of the incidence of adventitial infiltrations in the coronary and non-coronary cases are shown in Table I and Fig. 2.

Of the 101 coronary cases 80 per cent showed adventitial infiltrations, whereas these were present in only 29 per cent of the 59 control cases. This difference is in itself of high statistical significance even though many of the controls were selected as potential " positives," after preliminary observations had indicated that certain types of non-coronary deaths appeared to be associated with the incidence of the adventitial foci.

TABLE I

DISTRIBUTION OF 160 CASES CLASSIFIED BY "MODE OF DEATH" AND DEGREE OF ADVENTITIAL INFILTRATION

Degree of infiltration	Coronary deaths						Non-coronary deaths	
	Group I		Group II		Group III			
	Cases	%	Cases	%	Cases	%	Cases	%
O	4	8·5	9	26·5	7	35	42	71·0
I	23	49	17	50	6	30	11	18·7
II	17	36	6	17·5	6	30	5	8·6
III	3	6·5	2	6	1	5	1	1·7
Total ..	47		34		20		59	

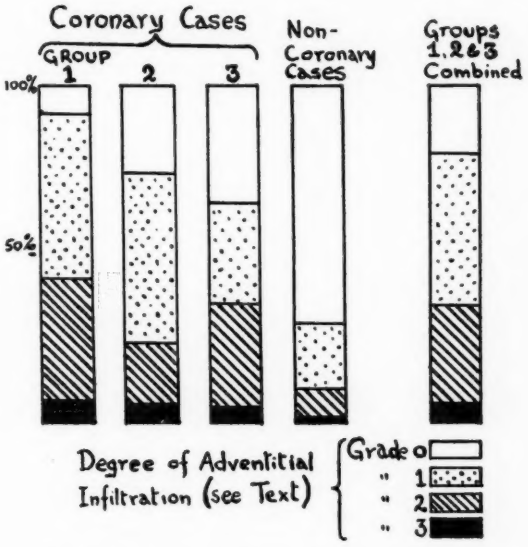

FIG. 2.—Percentage incidence of adventitial infiltration.

Separation of the coronary cases into groups as previously described, showed a significant difference in the incidence of infiltrations. In Group I (acute coronary deaths without infarction), 44 of 47 cases showed infiltrations, i.e. over 90 per cent positive. In Groups II and III respectively, 25 of 34 cases, and 13 of 20 cases were positive (74 and 65%). This difference between Groups II and III is not significant.

No significant relationship was established between the degree of coronary atheroma and the incidence of adventitial infiltrations. In Table II the distribution of atheroma grades in those cases showing infiltrations are compared. The non-coronary positives show a significantly lower degree of atheroma than the coronary positives. No correlation was found with sex or age distribution, adventitial infiltrations being found in subjects between 33 and 91 years of age.

TABLE II

ATHEROMA INCIDENCE IN " CORONARY " AND " NON-CORONARY " CASES SHOWING ADVENTITIAL INFILTRATIONS

Atheroma grade	Coronary		Non-coronary	
	Cases	%	Cases	%
1	4	5	5	29
2	32	39	8	47
3	45	56	4	24

The inferences drawn from the statistical analysis are that the adventitial infiltrations are not related to the degree of coronary atheroma but rather to the mode of dying.

If the atheroma itself is not responsible for the infiltrations some useful information on the ætiology of these adventitial lesions might be obtained by reference to the modes of death in the non-coronary cases in which such lesions occurred. Could some common denominator be found in these cases that had died of diverse causes, and if so could this same factor be held to be responsible to some extent, for the fatal outcome of the cardiac disease in the coronary group?

Of the 59 non-coronary cases 17 showed the presence of adventitial infiltrations and in each of these cases an anoxic element was associated with the mode of death. Infiltrations were present in three of the six cases of carbon monoxide poisoning, and three of the five cases of hanging and strangulation. Of the 19 cases of intracranial lesions eight were positive, the majority being cases of massive cerebral hæmorrhage. The anoxic element in fatal coma associated with cerebral hæmorrhage is well recognized clinically, and it is suggested that the high incidence of infiltrations in the adventitia of the coronary arteries in such cases (six out of ten) is a reflection of the respiratory insufficiency. By contrast none of the six cases of subarachnoid hæmorrhage showed infiltrations. It is considered that this apparent discrepancy is explained by the difference in duration of the terminal coma, which in the cerebral hæmorrhage cases was invariably a matter of several hours, whereas in the subarachnoid hæmorrhage cases death generally occurred in a matter of minutes. In one case a large area of cerebral softening and œdema produced a similar clinical picture to that of a cerebral hæmorrhage and this too was " positive." One patient died of broncho-pneumonia after several hours of progressive cyanosis and respiratory distress. This case was " positive." The other two (negative) cases of pneumonia were clinically toxæmic deaths.

Of the hæmorrhagic cases two of the five were " positive " the remaining negative ones died almost instantaneously following massive hæmorrhages.

The lesions in a patient who died of respiratory failure due to acute bulbar poliomyelitis were classified as negative as no focal infiltrations were present in the coronary adventitia, but there was in fact an atypical diffuse adventitial infiltration.

DISCUSSION

It is suggested that focal adventitial infiltrations in the coronary arteries of the non-coronary cases are associated with, and in fact caused by, a state of anoxia. This hypothesis is supported by the findings of Gruenwald (1949) who reported changes in the coronary arteries, including adventitia infiltrations, in 21 stillborn or newborn infants, all of whom showed varying degrees of asphyxia.

If anoxia is considered responsible for adventitial infiltrations in these non-coronary deaths, it can reasonably be assumed to play a local role in the coronary group, as it was only in the coronary deaths that these adventitial lesions were found in the absence of generalized anoxia.

Examination of the incidence and microscopic appearances of the adventitial foci does not support suggestions that they are essentially a part of the atheromatous process in itself or that they are due to local inflammation or toxæmia. The dissociation of the incidence of infiltrations with that of atheroma has already been remarked upon, and one does not find such adventitial lesions in atheromatous areas of the arota or limb arteries.

It is suggested that local anoxia occurs in the fatal coronary cases as a result of spasm of the vessels, particularly the small vessels of the coronary adventitia. Specific localization in the heart can only be partly explained by suggesting a disproportionate degree of anoxia due to the high oxygen requirement of the heart muscle, as infiltrations are not found where the oxygen tension might be assumed to be lowest, that is, in association with the small intramyocardial branches of the coronary arteries. This suggests that the local perivascular anoxia is associated with an active participation of the vessels concerned, namely spasm.

The micro-anatomical relationships of the adventitial foci to the coronary arteries do not support the view that the infiltrations are part of the atheromatous process. The foci are often found at sites corresponding to the lesser degree of atheroma in a particular vessel, and are often quite isolated from the artery itself. Even when quite large, the lesions do not display any signs of organization or fibrosis which suggests that they are related to the terminal mechanism responsible for death.

The hypothesis that infection might be the cause of the infiltrations does not stand up to close examination. No doubt mycotic infection of coronary arteries can, and does occur, but it is considered very improbable that such a factor was present in the lesions in 80 per cent of the present series of 101 cases of acute coronary deaths. On similar grounds, the views that generalized primary inflammation (Saphir and Gore, 1950) or intoxication (Nelson, 1941) may be responsible for the lesions, appear to be untenable and also they fail to explain the localization to the coronary vasa vasorum, whereas polyarteritis nodosa shows no such localization.

Karsner and Bayless (1934) described changes in the coronary arteries in association with rheumatic carditis. The histological appearances, however, differed from those of the adventitial lesions described in this paper, and in the two cases in the present series in which there was a clinical history or pathological evidence of previous rheumatic carditis no adventitial infiltrations were found.

Albertini (1943) has described a condition in young adults which he called " Arteritis chronica stenosans coronariæ " and this has been further described by Walthard (1942): perivascular and perineural infiltrations were found which appeared to be similar to those described in the present series. These authors considered that the lesions were not atheromatous, but were due to a metastatic mycotic arteritis due to focal infection, and that the pathological process was initially an adventitial change which spread to the media and intima. It is improbable that this explanation holds true for the findings in the present series and it is disputed whether this arteritis chronica stenosans coronariæ is indeed a specific entity. That spasm, rather than anatomical change, is responsible for many of the clinical symptoms of coronary insufficiency is demonstrated by the symptomatic relief in cases of angina, on administration of vasodilator substances such as nitrites. Interference with the sympathetic nerve pathways by ganglionectomy also improves the prognosis in experimental coronary occlusion in animals (Cox *et al.*, 1936, and Shauer *et al.*, 1937). The association of the adventitial infiltrations with the vasa vasorum of the larger coronary arteries and not with the smaller branches is in agreement with Woollard's (1926) findings that the larger coronary arteries are predominantly innervated by branches of the sympathetic nerve whereas the smaller branches are mainly supplied by the vagus.

Green (1935) showed that profound stimuli from many parts of the body can cause reflex constriction of the coronary arteries which may reasonably be assumed to be possible even in the painless and silent cases of coronary occlusion and myocardial infarction, by means of local ganglion reflexes or even axon reflexes.

In fatal cases, the majority of which may show no significant organic lesion, it is suggested that intense spasm of the vasa vasorum of the coronary arteries causes local anoxia in the adventitia and that this latter state may be recognized by lymphocytic infiltrations. The exact mode of formation of these infiltrations or the time required for their formation is not known, but the cells appear to be of intravascular origin and it is probable that their appearance is preceded by yielding of the vascular spasm to paralytic dilatation. If this is correct it would appear that many of the apparently

sudden or instantaneous cardiac deaths are really the terminal phases of silent " anginal attacks " which may have been present for a considerable time, possibly several hours.

Should this hypothesis, of the dominant role of spasm in the fatal outcome of coronary disease receive confirmation, it might be of advantage to review the methods of treatment of acute coronary insufficiency, particularly in regard to the drugs that depress ganglionic activity.

Summary

The incidence of focal adventitial infiltrations in coronary arteries and its relationship to the degree of atheroma and mode of death, in 160 cases, are discussed.

These lesions are considered to be caused by local anoxia as a result of reflex vascular spasm.

It is considered that in the absence of a state of generalized anoxia these infiltrations may be regarded as an indication that coronary artery disease was directly associated with the cause of death and not merely an incidental condition.

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THE PATHOGENESIS OF VALVULAR THICKENING IN RHEUMATIC HEART DISEASE

BY

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Recently Magarey (1949, 1951) has shown the part played by repeated fibrin deposition in the pathogenesis of valvular thickening in rheumatic heart disease. He showed that fibrin deposited on the surface of a thickened valve became hyalinized, lost its fibrin-staining qualities, and became covered over by endothelium on which further fibrin might be deposited before the first was organized to fibro-cellular tissue. As many as three layers of fibrin in varying stages of organization were described. By implication (though not explicitly) he suggests that buried hyaline material in valves is usually or always buried fibrin, though he does not specifically discuss the question of how to decide whether buried homogenous acidophil material is altered fibrin or a degenerative change in underlying collagen. He dealt with changes in the chronic stages of the disease and did not consider at length the part played by vegetations in acute rheumatic valvulitis or the changes preceding thrombus deposition. It is the purpose of this communication to suggest that all such collections of homogeneous acidophil material found in rheumatic valves are organizing or incompletely organized thrombotic deposits and that there is no compelling histological evidence that they are ever degenerated swollen collagen or a ground substance change. A further conclusion is that the myxomatous swelling associated with fibroblastic proliferation that is seen in acute rheumatic valvulitis is not a precursor of so called fibrinoid degeneration but a result of rapid organization of thrombus. In addition, Magarey's views on the importance of thrombus deposition in the thickening of valves and in the stenosis of valve ostia are confirmed and extended to include the stage of acute valvulitis. During the study particular attention was paid to the lesions preceding thrombus deposition.

Pathogenesis of Valve Thickening. The commonly accepted view of the pathogenesis of the thickening of valve cusps is that it is due to an acute valvulitis often, but not necessarily, with inflammatory cell infiltration, œdema, degeneration of collagen, marked fibroblastic proliferation, and subsequent cicatrization. Koniger (1903) emphasized the presence of marked swelling of subendothelial connective tissues which had undergone a "homogenizing hyaline necrosis" (called by Klinge, (1933) "fibrinoid degeneration"). Coombs (1911, 1924) stressed the part played by submiliary nodules which he identified with those described by Aschoff and Tawara (1906).

In addition to the above-mentioned writers, Gross and Friedberg (1936), Wilson (1940), and Murphy (1952), hold similar views. Gross and Friedberg (1936*a*) also emphasize the part played by the incorporation of chordæ tendineæ into the valve cusps and mutual fusion of the chordæ and of cusps at the commissures, which is also mentioned by Rokitansky (1852), Rindfleisch (1872), Wilson (1940), and Brock (1952). Coombs denies that this happens in the case of the mitral valve, but allows that it occurs in the aortic valve. Magarey's views have been described; he points out that deposits lead to the fusion of chordæ to the distal surface of valve cusps with resultant secondary shortening of the chordæ. Brock (1952) suggests that mutual fusion of mitral cusps takes place at certain critical sites and that it does not occur progressively from the periphery towards the centre.

The Nature of the Lesion preceding Thrombus Deposition. Veraguth (1895) states that thrombus

deposition may occur when endothelial damage is the sole lesion or at the same time as inflammatory changes in the valve. The characteristic lesion of rheumatic endocarditis according to Koniger (1903) is deep homogenizing necrosis with œdema of the endocardium, precipitation of fibrin-like masses in the deeper layers of the subendothelium, and marked swelling which may project above the level of the endocardial surface; on this thrombus deposition may occur: leucocytic infiltration is not striking but proliferation of cells is.

Klinge's (1933) description is similar to Koniger's; he describes Aschoff nodes in the valve but does not indicate whether their occurrence is particularly associated with vegetation formation or not. Coombs (1909, 1924) describes a valvulitis and submiliary nodules which are groups or zones of large fibroblasts with some giant cells in a groundwork of fibrin; the fibrin is difficult to see in the myocardium, but in the endocardium there is often a central area consisting of nothing but fibrin with a sharp margin. He suggests that the nodules may sometimes be formed by necrosis of the endothelium of a newly formed blood vessel with thrombosis therein and marked peri-vascular proliferation of fibroblasts. Although he equates these nodules with those described by Aschoff and Tawara (1906) these latter authors do not refer to the presence of fibrin. Judging from the illustrations Coombs seems to be describing two kinds of nodules, viz. Aschoff nodes (in which fibrin is very rarely present) and some other form of nodule forming round fibrin or fibrin-like material such as that described by Koniger or Klinge. Veraguth, in talking of acute endocarditis mentions that if superficial organization of a vegetation occurs the most superficial layer of the cusp appears undermined by the thrombus or raised up by it. Almost complete organization of such a thrombus would look like those of Coombs' submiliary nodules which contain a well-defined area of fibrin or like the deep homogenizing (fibrinoid) necrosis of Koniger and Klinge.

Leary (1932) and Gross and Friedberg (1936) believe that superficial degeneration of cells is the lesion that precedes vegetation formation, while the latter agree with Klinge that acidophil swelling of collagen precedes fibrin deposition.

The Nature and Structure of Vegetations

These have been variously described as consisting of fibrin, fibrin and platelets, platelets only, connective tissue or a mixture of these elements (Veraguth, 1895; Coombs, 1924; Clawson, 1926; Grant and Wood, 1928; Murphy, 1952). Swollen acidophil collagen is a further constituent according to Koniger (1903), Klinge (1933), Bulloch (1906), and Gross and Friedberg (1936); it is usually said to be deep to the thrombotic element. Swift (1925) thinks that vegetations may be formed by submiliary nodules ulcerating through the endothelium.

Material and Methods

Twenty-nine hearts with rheumatic mitral valve disease were examined, of which 26 showed marked or gross valvular deformity. One showed only moderate thickening of the cusps without gross deformity or narrowing of the valvular orifice; the myocardium contained Aschoff bodies and death was due to acute pulmonary œdema. Two were cases of acute rheumatic pancarditis in children aged 8 and 9 respectively with Aschoff bodies in the myocardium. Thickened aortic valves were examined in five of the chronic cases and so were moderately thickened mitral valves present in two hearts with calcific aortic stenosis: these valves were vascularized and although Koletsky (1946) claims that all vascularized mitral valves are due to rheumatism, there was no unequivocal evidence of rheumatism (Aschoff nodes) present in the six blocks of the myocardium examined from each of these hearts.

The incidence and nature of surface deposits on these valves was determined by examining them with a hand lens, and with a binocular dissecting microscope. Frozen sections of suspicious areas (taken at random intervals) were then cut and stained with hæmatoxylin and Sudan 3, hæmatoxylin and eosin, orcein elastic stain, and Mallory's phosphotungstic acid hæmatoxylin (M.P.A.H.). Toluidine blue 1 per cent was used on selected sections. Frozen sections were used as these showed up the texture of tissues better than paraffin embedded ones. Contiguous blocks were embedded in paraffin and stained with similar stains (except Sudan), picro Mallory, and Weigert, elastica and Gram. Selected sections were stained with Foot's reticulin stain, Weigert's fibrin stain and periodic acid Schiff (P.A.S.). Other affected valves were examined in the same way, but no effort was made to discover the absolute incidence of deposits which were found in 29 out of 31 mitral valves and four out of five aortic valves. Buried Lambl's excrescences were seen in nine cases.

Sites of Deposits

They were found most commonly in the commissures between thickened cusps on the contact line of the valve and on the extreme tip; they were less commonly found on other parts of the proximal surface of the cusp, on the chordæ tendineæ especially near the insertion of those of the first order and in the pockets between chordæ and cusp. They lead to thickening and fusing of chordæ which then become part of the valve cusp and lengthen it. This phenomenon leads to a change in the contact line of the valve which moves distally as and if the valve so lengthens so that new generations of vegetations are laid down on a different site (see Gross and Friedberg, 1936). Fig. 1 shows a vegetation at the point of insertion of two chordæ into the cusp of a tricuspid valve; Fig. 2 is a

Fig. 1.—Tricuspid valve cusp, showing vegetations overlapping chorda insertions (A). × 5·5.

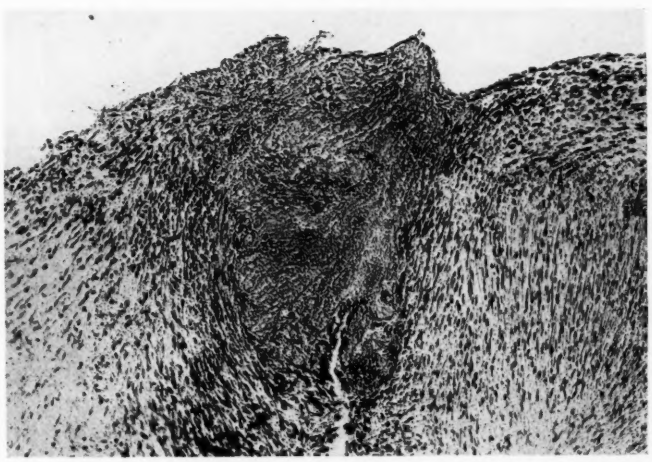

Fig. 2.—Frozen section through A of Fig. 1, showing fusion of chordæ by vegetation material. (Hæmatoxylin) ×100.

section taken through a line through A showing fusion of the chordæ by vegetation material. Fig. 1 shows them to be fused more distally also. When chordæ are inserted obliquely into the cusp as they are near the centre of both mitral cusps, their fusion together adds to the length of the cusp, the free edge of which may be made up of chordæ tendineæ.

In a case of acute rheumatic pancarditis deposited material was widespread on both surfaces of a mitral cusp and formed 5–10 per cent of the thickness of the cusp in some places.

Material deposited in the angles between the cusps (Fig. 4 and 9) and on the endothelial folds at that site in the mitral valve leads to gradual fusion of opposing cusps, mainly by a silting up process. At the same time fusion of the chordæ at these sites occurs and helps to prevent the cusps opening fully in auricular systole. In those valves that show the earlier stages of mitral stenosis, no evidence was found that fusion occurs first at certain critical points distant from the angles between the cusps, as suggested by Brock (1952).

The Structure of Vegetations and of the Tissue Underlying Them

Fig. 3 is a hæmatoxylin-stained section of a typical warty vegetation. There is recent fibrillary deposition on the surface, the layers deep to this are somewhat granular, and below that again they are homogenous. Lamination is clearly shown as is progressive organization from the base. The

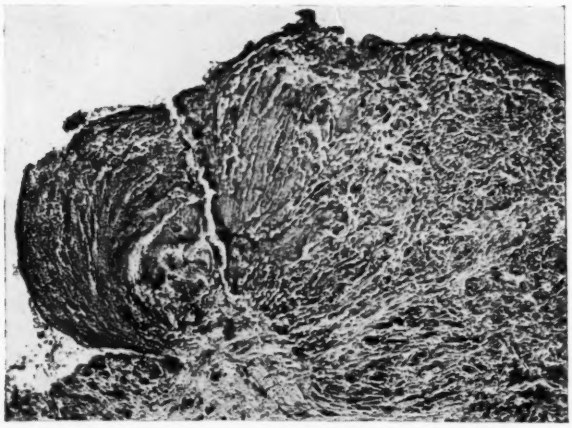

Fig. 3.—Frozen section of warty vegetation on aortic valve. It shows layering of older deposited material and the granular appearance of the most recent deposit (Hæmatoxylin and Sudan 3) ×140.

material of the vegetation is acidophil (in hæmatoxylin- and eosin-stained sections) and stains partly fibrin positive and partly fibrin negative. Magarey suggests that deposits are entirely of fibrin, but in very recently deposited material there are two elements discernible, viz. a granular fibrin negative portion and a fibrillary fibrin positive one, fibrin itself. Mallory's phosphotungstic acid hæmatoxylin (M.P.A.H.) gives the most consistent reaction. As homogenization takes place, with the increasing age of the deposit, these two differently staining elements are still visible. The fibrin negative portion predominates in vegetations, especially those which are acute, the fibrin positive portion in ordinary mural thrombi and sometimes in the deposits on valves with much collagen. The staining reactions of vegetations *vis à vis* fibrin were felt to be explicable on the basis that there were two different constituents. The granular material is usually considered to consist of platelets, though there seems to be no absolute unequivocal evidence that this is so. Zucker (1949) gives a discussion of the part played by platelets in thrombosis.

To compare with Fig. 3, Fig. 4 is a frozen section stained with hæmatoxylin of the commissure of a mitral valve; Fig. 5 is a hæmatoxylin- and eosin-stained section from the same block after it had been embedded in paraffin. Some granular superficial deposit can be seen in both of these sections which also demonstrate the difference between the texture of frozen and paraffin sections

FIG. 4.—Deposit in a commissure of the mitral valve. Frozen section. (Hæmatoxylin and Sudan 3) ×90.

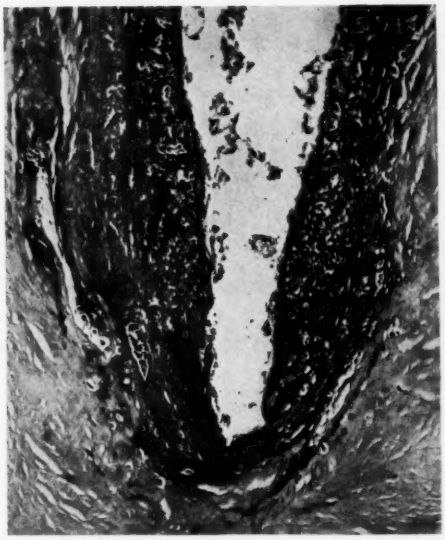

FIG. 5.—A neighbouring section to that shown in Fig. 4—paraffin embedded. (Hæmatoxylin and Eosin) ×90.

so stressed by Duguid (1952). These sections pose the problem of the nature of homogenous eosinophilic material often seen on the surface of valves or underlying the frankly thrombotic part of a vegetation. Some of the other writers who have been quoted believe that when this material is seen in deeper layers of the valve or in the base of a vegetation it is swollen degenerated collagen staining like fibrin (e.g. Koniger, 1903; Klinge, 1933; Coombs, 1924; Gross, 1936). An effort was made to decide whether such material was purely thrombotic (made up of fibrin and some other constituent, probably platelets), purely degenerative, or a mixture of the two. The latter view would follow from any hypothesis that accepted the occurrence of fibrinoid degeneration. It was found that in that part of the cusp away from the commissure this material never lay immediately deep to an intact superficial elastic lamina or even deep to coarse broken fragments of elastica where it might be expected to occur were it due to degeneration of deep tissues. Its occurrence deep to an elastic lamina in the region of the commissures cannot be held to be due necessarily to degeneration because of the large number of folds and pockets in these situations. In Fig. 4, for instance, there is an endothelial-lined cleft at A; if thrombosis occurred in this it might at first sight look as though it were deep degeneration. Thrombi were seen in pockets deep to elastic laminæ.

Another fact that makes it difficult to assess whether a lesion is a deep degeneration or a buried thrombus is the rapidity with which a thrombus may become covered by endothelium or even by a fibroblastic layer, as shown by Duguid (1952). Fig. 6 is a hæmatoxylin-stained frozen section from a valve showing active valvulitis with many Aschoff nodes; this shows endothelium growing over very recent deposit below which two further layers are distinguishable. From above downwards

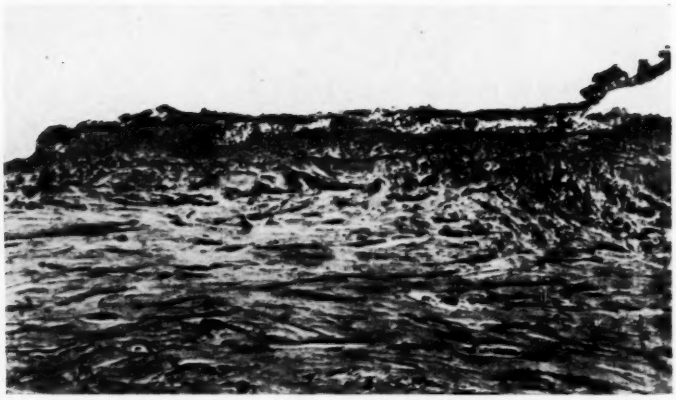

FIG. 6.—Layering of deposit on the surface of mitral valve, with overgrowing endothelium. Frozen section. (Hæmatoxylin) ×200.

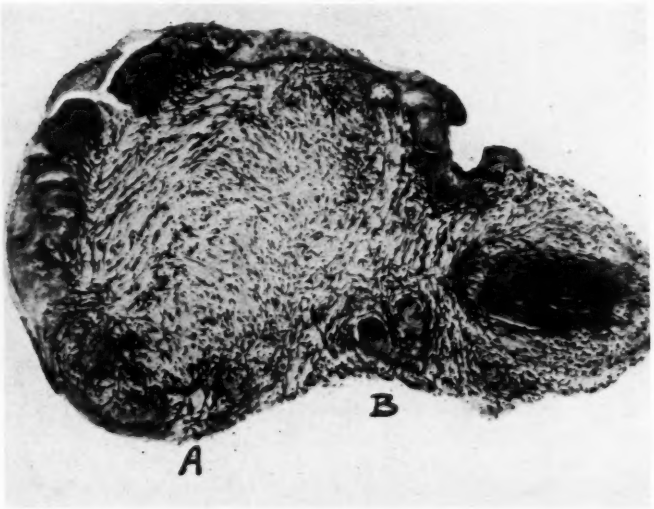

FIG. 7.—Chorda tendinea (seen on the right of the figure) and a vegetation showing surface deposit and overgrowing fibroblasts (A and B). Frozen section. (Mallory's phosphotungstic acid hæmatoxylin) ×55.

the layers show a change from a partially fibrillary loose textured appearance to a homogeneous hyaline one. These are the changes shown by ageing thrombus. It would be difficult to explain them on the basis of degeneration of subendothelial connective tissue. In neighbouring sections further from the edge of the lesion, endothelium was not yet present. Fig. 7 is a frozen section, stained with M.P.A.H. of a vegetation on a chorda tendinea. The portion on the right is the obliquely cut chorda, the rest organizing vegetation. At A it can be seen how fibroblasts tend to

grow over lesions, while at B are two areas of buried thrombus, which have the appearance described by Coombs as those of submiliary nodules in the endocardium.

In lesions such as that shown in Fig. 4 and 5 one wants to know whether the superficial layer of acidophil material is all thrombus, all degenerated collagen, or a mixture. The paraffin section, Fig. 5, gives an appearance that might be interpreted as a degenerative lesion in connective tissue, together with a certain amount of recent superficial granular deposit. On the other hand, in the frozen section (Fig. 4) the surface material seems to be quite clearly defined from the underlying tissue and certainly gives the impression of being superimposed on it. Lamination is just visible towards the apex of the commissure, but it is more clearly shown in Fig. 8, a higher powered view

FIG. 8.—Neighbouring portion of valve shown in Fig. 4 and 5. Frozen section. (Mallory's phosphotungstic acid hæmatoxylin) ×160.

of a neighbouring part of the same section. This also shows more clearly the granular or amorphous fibrin-negative material deposited on the surface, organization from below with areas of fibrin staining material in the deeper layers of the valve, and entrapped groups of red cells clumped together. Both show the fibrinoid and non-fibrinoid reactions of vegetation thrombus. The presence of surface deposit, of lamination, and of entrapped red cells below the surface, which may all occur in typical verrucæ, suggests that successive layers of thrombus are laid down one on the other to form this acidophil layer. On this hypothesis it is easy to explain the underlying patches of fibrinoid or partially fibrinoid material which occur in Fig. 8; they are buried thrombus not yet organized; it is unnecessary to postulate any degenerative change to explain the appearances. These patches of deeper homogenous material are P.A.S. positive, a staining reaction that occurs in ageing thrombus. Is it reasonable to suppose that thrombi can be buried far below the surface without becoming converted into connective tissue? In Fig. 8 it can be seen that organization is being carried out by relatively few cells and that a dense collagenous tissue is being formed. This paucity of cells might well explain the presence of deeply buried thrombus such as the deeply staining material in the top, left-hand corner of Fig. 4; as organization appears to be more rapid and complete when cells are plentiful there is no compelling reason to suppose that such tissue is degenerative rather than "buried" once it is accepted that incomplete organization of successive layers of deposited thrombus will give such an appearance. That the burying effect occurs in more acute lesions has been shown in Fig. 7.

The presence of metachromasia in such myxomatous-looking tissue as is shown in this figure has been held to be a pre-fibrinoid degeneration change (Altshuler and Angevine, 1949), but this is also

found in recently formed tissue as shown by Tamayo and Ihnen (1953), who demonstrated its presence in healing wounds. In this study it was also found in organizing verrucæ; neither this nor the presence of a myxomatous appearance is of any value in distinguishing between degeneration and recent formation. The same remarks apply to the presence of fine elastica fragments which are held by Gross and Friedberg (1936) to indicate degenerative changes; an indistinguishable appearance is found in organizing mural thrombi, and P.A.S. positive tissue may also be present in such situation. The cellularity of a lesion was not a reliable guide as to whether it was degenerative or organizing because in acellular portions of the heart organization is carried out by very few cells, and relatively hyaline acellular tissue may be formed. The occurrence of necrotic changes in cells bore no constant relationship to acidophil homogeneous material.

In view of Coombs' description of submiliary nodules, a comparison of Aschoff nodes and valve lesions was carried out in order to see if this shed any light on the nature of deeply buried acidophil tissue. It is reasonable to suppose that in rheumatic heart disease the fundamental lesion in the connective tissue of the myocardium is the same as that in the valve; Coombs, for instance, describes submiliary nodules in the myocardium and in the endocardium. If myocardium and valve lesions are identical there should be comparable changes in valve cusp and myocardium. Aschoff nodes were present in 12 of 23 hearts examined for them; fibrin staining material was only very rarely seen and then it was fragmentary in character and never took the form of clearly defined areas of acidophil material. Many of the myocardial Aschoff nodes contained myocardial fibres in various stages of degeneration and it was difficult sometimes to distinguish these from fibrin. In the Aschoff nodes seen in valves, collagen fibres appeared to be swollen and fragmented in the frozen and paraffin sections, but they never showed the texture or staining reactions of vegetation material, they never stained like fibrin, and they were not associated with areas of clearly defined swollen acidophil material. It therefore appears doubtful whether the homogeneous acidophil lesions deep in a rheumatic valve can be the same sort of lesion as that which forms the basis of the Aschoff node. The former can all be explained as thrombi which have been incorporated into the valve; the latter is a cellular reaction to some form of tissue damage.

In many recent vegetations the base is formed by recently organized fibrous or fibro-elastic material (as in Fig. 4 and 8) in which the cells may be relatively scanty. This may occasionally give rise to the presence of collagen fibres ending blindly in the vegetation material; this does not necessarily indicate that the vegetation consists of degenerated collagen (Allen and Sirota, 1944). It is more probably due to incomplete organization such as would occur if there were too few cells present or if there was slow necrosis of the organizing cells. In organizing lesions some of the fibroblasts may show pyknosis which is not accompanied by anything suggestive of "fibrinoid" degeneration. As is well known, necrosis may also affect the endothelium growing over the surface of thrombus, as well as normal endothelium. In a relatively acellular area cell death may lead to marked slowing of organization giving the appearance shown in Fig. 9. This sort of lesion (called by Allen and Sirota "degenerative verrucal endocardiosis") is relatively common in old thickened valves though it may occur alongside more cellular lesions. The texture and staining reactions of these vegetations seem to be the same as those of vegetations which are more cellular. This one shows the lamination that is present in acute warty vegetations. It seems unnecessary to postulate that some of these vegetations are due to degenerated swollen collagen and others due to thrombotic deposits as do Allen and Sirota (1944) and Gross and Friedberg (1936). If organization (i.e. conversion of fibrin to collagen) were slow or non-existent, a thrombotic type of vegetation would eventually look like the type they call degenerative. The thin, deeply acidophil hyaline strips which occur on the surface of a valve can be explained by the same mechanism of incomplete, delayed or even absent organization. Barnard (1953) has shown that artificially produced fibrin emboli may be incorporated into the wall of a pulmonary artery and remain unorganized for a time even when cells are plentiful. He also shows that the elastica lamina deep to these fibrin emboli becomes fragmented, so that if such an appearance is found deep to deposit on a valve cusp, it does not necessarily mean that degeneration has preceded the deposition.

FIG. 9.—Mitral valve with acellular hyalinized vegetation. Frozen section. (Mallory's phosphotungstic acid hæmatoxylin) ×55.

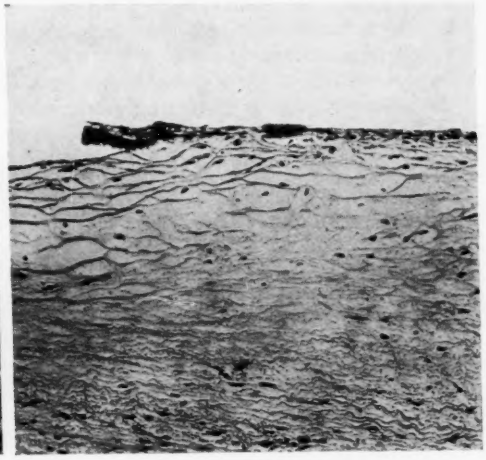

FIG. 10.—Tricuspid valve, showing superficial degenerative changes and fine deposit. Paraffin embedded section. (H and E) ×140.

FIG. 11.—Recent deposit on mitral valve, showing pyknotic changes in underlying nuclei. Paraffin embedded section. (H and E) ×275.

THE CHANGES PRECEDING THROMBUS DEPOSITION

In the course of the investigation an attempt was made to determine what change immediately preceded vegetation formation. Fig. 4, 8, 10, 11, and 12 show the various conditions associated with the presence of recent deposit which was found on the following structures.

1. On degenerating endothelium (Fig. 10).

2. On collagenous tissue in which the surface layer of cells showed only minimal pyknotic changes (Fig. 11).

3. On relatively acellular collagen denuded of endothelium (Fig. 12).
4. On mechanically damaged partly calcified collagen.
5. On torn valve tissue (once only).
6. On pre-existing vegetation material (Fig. 3, 4, 6, 7, and 8).
7. On a basis of connective tissue with proliferating fibroblasts.

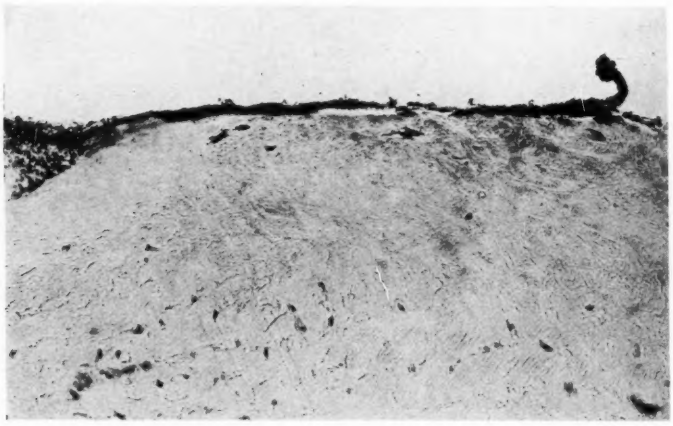

FIG. 12.—A deposit, partly fibrillary and partly condensed, on a valve cusp devoid of endothelium. Cellular "ghosts" are seen in underlying tissue. Frozen section. (Hæmatoxylin) ×40.

In these photographs it can be seen that neither fibrinoid change nor underlying inflammation is necessarily present at the onset of thrombus deposition. Damage limited to the endothelium or absence of a well defined and differentiated normal endothelium seems to be sufficient to allow deposition. Although deposits are commoner and more widespread in the inflamed cusp, inflammatory changes, e.g. Aschoff nodes, may occur deep to a well defined endothelium without there being any thrombus deposition. Pyknotic changes may also occur in subendothelial tissues without evidence of overlying endothelial damage or of thrombosis necessarily occurring. Deposits were never seen on completely normal well-defined endothelium.

Sometimes pyknotic changes and karyorrhexis were seen in the endothelium (Fig. 10) or in the cells invading recent deposit. It was thought that this represented one of the essential lesions predisposing to thrombus deposition, but it was later realized that this sort of change occurs almost entirely at sites of severe mechanical damage. As the trauma of valve closure does not usually cause visible endothelial damage, the occurrence of such changes at closure sites indicates the action of a noxious agent in addition to the trauma itself.

DISCUSSION

It has been shown that swollen acidophil material in a valve cusp is always explicable as incorporated thrombus. A problem that arises is whether the inflammatory changes necessarily precede thrombus deposition in the acute and subacute stages, or whether they merely accompany it or result from it. In the acute cases studied it was difficult to tell which was primary inflammation and which was the result of organization of repeated widespread thromboses. Inflammatory infiltration of cells such as polymorphs and plasma cells was slight; lymphocytes were moderately plentiful, but proliferation of fibroblasts was the main change. Œdema is difficult to diagnose unequivocally histologically and can be mimicked by the myxomatous appearance in organizing

thrombi (Fig. 7). Many of the fibroblasts seen were large and deformed with many processes, the so-called Aschoff cells; they may be basophilic or amphophilic and multinucleated. They are commonly seen invading the base of vegetations and were present even in cases of long-standing disease with advanced changes. In some cusps Aschoff nodes themselves were seen away from the main areas of vegetation formation and also in tissue that appeared to be a recently organized warty vegetation. The cellular reaction that seems most characteristic of rheumatic valve disease is the presence of Aschoff cells. These cells are almost always present in relationship to organizing deposits and are found mainly in the immediate vicinity of the thrombus or burrowing into it. In lesions such as those shown in Fig. 4 and 8 they may only be present in ones and twos; they become more difficult to find in the older more thickened and less cellular valves. They are also found in the valve cusp Aschoff nodes and here are related to what appears to be fragmented connective tissue without fibrinoid change. These cells seem to occur as a reaction either to tissue damage or to thrombosis; there is no indication that they are ever the forerunners of thrombus deposition, rather do they follow it.

The effect of organization of successive thrombotic deposits especially when widespread as in the acute (i.e. cellular) stages, will be the production of fibroblastic proliferation with vascularization of the new-formed tissue and perivascular lymphocytic cuffing such as is seen around the new vessels formed in relation to organizing mural thrombi. On the surface of some warty vegetations when organization is nearly complete, fibroblasts take up a palisade appearance. This is one particular pattern taken up by organizing cells in a particular situation and not a primary event as Leary (1932) suggests, though necrosis of such recently organized tissue may occur if it is subjected to trauma. Whether it becomes necrosed because it is intensely proliferating or because of damage due to the disease process is uncertain.

It is difficult to see the above described inflammatory changes in rheumatic valvulitis as the precursor of thrombus deposition. It seems rather that thrombus deposition can be initiated by a very minimal lesion of the surface endothelium of the valve, which may damage the superficial layers of cells enough to cause those that are mechanically damaged, such as those on the closure line, to become necrotic. At the same time as deposition occurs there is a cellular reaction of fibroblasts and Aschoff cells. As these cells invade the thrombus, more thrombus is commonly laid down on the surface. New growth of capillaries and small round cell infiltration follow. (Thrombosis in these new-formed capillaries is very common in the acute phase.)

In considering the problem of the nature of the lesion that precedes thrombus deposition, one is hampered by the fact that the valve cusps are already so changed even in the earliest cases that it is impossible to distinguish normal valve tissue from newly added tissue. However, one striking feature is the frequency with which thrombus is seen on a basis of connective tissue containing proliferating fibroblasts with many, few, or no Aschoff cells. It is as though there were some reaction between the connective tissue and the surrounding blood leading to continuous deposition of material. Whether the underlying tissue is relatively acellular collagen or myxomatous-looking intensely-proliferating tissue containing developing capillaries does not seem to matter very much. It is possible that changes in the coagulability of the blood are more important than changes in the underlying valve. However, there must be some phenomenon occurring in the valve to explain the Aschoff node lesions and the fact that deposition occurs mainly on valves, albeit at other sites in the circulation as well. In addition to these there must be some explanation for the fact that deposits are more intense and more widespread on younger more acute valvular lesions. It is true that sometimes the size of individual vegetations is greater in old thickened rheumatic valves, but this is partly due to the fact that the valves are less cellular and thrombotic deposits are more slowly organized. It remains true that in rheumatic valve disease the lesion in the valve that leads to thrombosis is not usually histologically visible.

A suggested sequence of events in acute valvulitis is therefore: œdema, perhaps with Aschoff node formation, and relatively minor cellular infiltration—minimal damage to endothelium—widespread thrombus deposition—rapid organization with fibroblasts and Aschoff cells—further

thrombosis—vascularization and perivascular lymphocytic infiltration. This scheme is instead of: œdema, sometimes cellular infiltration—proliferation of fibroblasts and capillaries—fibrinoid degeneration of collagen with swelling and overlying endothelial necrosis—thrombus deposition and organization.

In subacute and chronic lesions the differences are mainly those of degree; fibroblastic proliferation and vascularization become less intense, Aschoff cells less prominent, and fewer cells are involved in the conversion of thrombus to new connective tissue which is much more hyaline. Fig. 6, 8, and 11 show three stages of decreasing cellularity. The more hyaline tissue contains more fat and elastic laminæ may become very thick and sometimes have a granular appearance like the elastic tissue in Lambl's excrescences (Magarey, 1949). Although in the later stages the new-formed tissue is hyaline from the beginning, such tissue is of course also formed from connective tissue that was initially more cellular.

A remark must be made about old thickened valves where fragmentation of degenerate pale staining or calcifying collagen has formed a focus for thrombus deposition. Here the fragmentation, the avascularity and hypocellularity of the valve tissue may be the main factor in deposition. In common with more acute lesions there is the absence of endothelium.

It is impossible to say precisely what proportion of the thickening of valve cusps is due to deposited material. There are three ways in which the thickening may occur. (1) Cusps may be "blown up" as it were from within by imbibition of fluid or proliferation of cells throughout the valve or in parts of it, (2) they may be thickened from the surface by cells "piling up" on the free surfaces and growing out into the surrounding blood stream, or (3) material may be deposited on the surface and be organized. Sections have been seen that suggest the possibility of the second of these three mechanisms occurring; when plasma is caught up in pockets formed between cusps and chordæ and then coagulates, the growing processes of cells seem to be projecting into the coagulum. In the previous work reviewed, the "blowing up" effect was held to be the most important factor in thickening, until Magarey's paper. In support of the deposition theory it is significant that the greatest thickening of valve cusps is precisely at the place where vegetations are commonest, viz. on the free edge and the contact line. It must be remembered that the contact line of rheumatic valves is not a fixed point, but varies owing to factors that tend to lengthen and shorten the cusp. The tip itself comes to be made up entirely of added material and incorporated chordæ.

When it is considered that deposits can be found at almost all stages of rheumatic valvular disease if they are looked for carefully enough, that they may be very widespread, that the disease may go on for many years, and that individual lesions may take only a week or two to organize completely, it seems not unreasonable to suggest that a major part of the thickening that occurs is due to these deposits even though the other possible mechanism may also be involved in varying degree.

Summary and Conclusions

The high incidence of thrombotic deposits on rheumatic valves is confirmed. They were found on valves at all stages of the disease, though there were fewer of them in the older lesions. They consist of fibrin and some other constituent, probably platelets.

The frequency of these deposits, their widespread nature in the acute stage, and the fact that all ages were often found in any one cusp support the hypothesis that they are responsible for much of the thickening in rheumatic valvular disease.

They are also thought to account for the mutual fusion of chordæ, for the fusion of chordæ to valve cusps, and for the incorporation of chordæ tendineæ into valve cusps.

In acute rheumatic valvulitis there is no certain method for distinguishing partially organized deposits from so-called fibrinoid degeneration of collagen; the idea of such degeneration may be a superfluous concept. These deposits are very widespread so that most of the actively proliferating tissue in these valves could well be due to the organization of successive thin deposits rather than a primary proliferation, especially as organization of a deposit often gives rise to a myxomatous

appearance indistinguishable from an appearance of swelling due to œdema. It is likely that a large part of such myxomatous material in acute lesions is organized thrombus.

Neither valvulitis, in the sense of a primary proliferative lesion, nor a pre-existing degenerative lesion of collagen or ground substance is a necessary pre-requisite of thrombus deposition. This may occur when endothelial damage or absence appears to be the sole lesion.

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CORRECTED TRANSPOSITION OF THE GREAT VESSELS

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The purpose of this paper is to report an example of the rare developmental anomaly corrected transposition of the great vessels and to discuss the concept of corrected transposition.

NOMENCLATURE

It is essential to define certain terms used in this report as there is much variation in usage.

Transposition. In transposition of the great vessels with the cardiac chambers in the normal position, the arterial trunks are altered in their relationship to each other at their origin from the ventricles so that the aorta is moved to a varying degree to the right and front. The general result is that the aorta, being thus moved to the right and anteriorly, is now more closely related to the right ventricle, and with the exception of the mildest degree of transposition the aorta comes to lie in the path of unaerated blood from the right ventricle. Transposition is generally ascribed to abnormal growth or absorption of the bulbar region of the primitive heart tube which interferes with the movement backwards and to the left (clockwise torsion) that normally takes place in this region. The embryological basis of transposition and the classification of various types have been extensively discussed (Spitzer, 1923; Harris and Farber, 1939; Bremer, 1942; Lev and Saphir, 1945; Lev, 1953).

Inversion. When there is inversion (situs inversus) as opposed to the normal position (situs solitus), an organ (or part of an organ) is formed as a mirror image of the normal with alteration of relation in the transverse plane but not in the antero-posterior plane. Inversion probably occurs at a very early stage of development but the embryological basis is unknown.

Inversion and transposition are thus distinct anomalies, one essential distinguishing feature being that inversion preserves the antero-posterior relations and transposition changes them. The two anomalies may co-exist, however, and the combination of inversion and transposition is much more frequent than would be expected by chance. Such combinations are best designated inverse transposition, and inverse counterparts of most types of transposition have been recorded (Spitzer, 1923 and 1929; Pernkopf, 1926).

Identification of Cardiac Chambers. In cases of inverse transposition individual cardiac chambers cannot be identified by their position, attached vessel, valve or by the type of blood conveyed. The only satisfactory routine method is to designate a chamber according to the following structural features as outlined by Lev (1954).

(1) The right atrium presents a limbus and fossa ovalis on its septal surface.

(2) The left atrium presents on its septal surface the irregular configuration of the septum primum as it is adherent to the septum secundum.

(3) The right ventricle presents a sinus and a conus divided by the crista supraventricularis. Its posterior septal surface is trabeculated and contains a variable number of papillary muscles.

(4) The left ventricle is without a conus. Its septal surface is only slightly trabeculated and contains no papillary muscles.

Corrected Transposition. Corrected transposition is a term which has been used in several senses. Its meaning can best be elucidated by examining the several types of inverse complete transposition.

In complete transposition (crossed or type 3 of Spitzer) in situs solitus the aorta arises from the right ventricle in an anterior position and receives unaerated blood: the pulmonary artery arises from the left ventricle posteriorly and receives aerated blood. Theoretically inversion may occur in any part of the cardiac tube (bulbar, ventricular, or sino-atrial region) so that eight types of complete transposition result and these are represented diagrammatically in Fig. 1. A1 shows complete transposition in situs solitus and A2 complete transposition in situs inversus: it will be seen that in each case the aorta arises from the right ventricle and receives unaerated blood. In A3 and A4 the aorta arises from the morphological left ventricle but receives unaerated blood; hence it can be regarded as "corrected" anatomically but not functionally. B1 and B2 show both functional and anatomical correction, the aorta arising from the morphological left ventricle and receiving aerated blood. In B3 and B4 the aorta arises from the morphological right ventricle but receives aerated blood; hence it is corrected functionally but not anatomically.

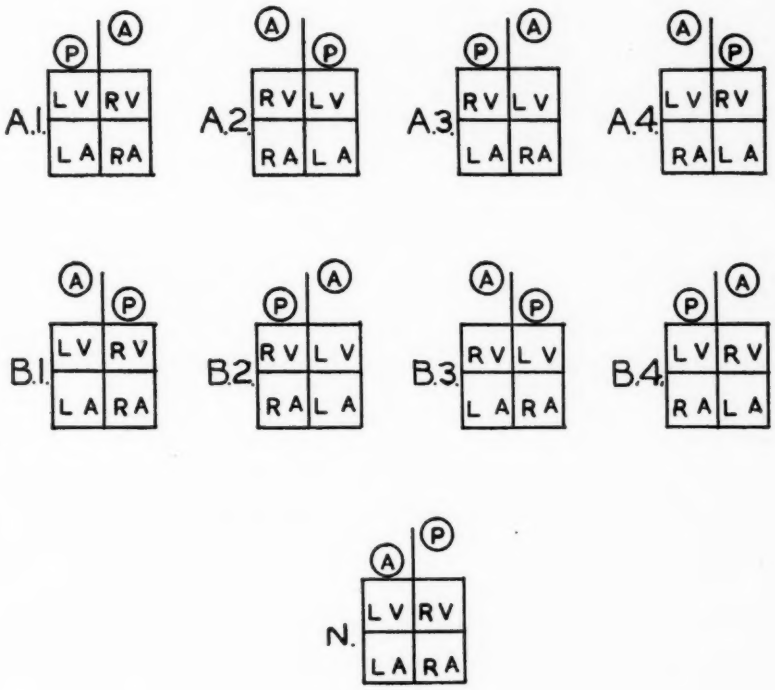

FIG. 1.—Diagram illustrating the various types of complete transposition. A similar diagram of a normal heart, N, is included below for the purposes of orientation. A indicates the aorta; P, the pulmonary artery; LA, LV, RA, and RV, indicate the *morphological* left or right, atrium or ventricle. A1 shows complete transposition in situs solitus; A2 shows the same in situs inversus; A3 shows ventricular inversion; A4 shows sino-atrial and bulbus inversion; B1 shows bulbus inversion; B2 shows sino-atrial and ventricular inversion; B3 shows bulbo-ventricular inversion; and B4 shows sino-atrial inversion (after Harris and Farber).

Thus, in cases of complete transposition of the great vessels, the term corrected transposition has been used in a functional sense to indicate that the aorta receives aerated blood, and in an anatomical sense to indicate that the aorta arises from the morphological left ventricle. In inverse forms of other types of transposition similar concepts of partial correction have been applied.

It would seem best, however, to restrict the use of the term corrected transposition to cases of functionally corrected complete transposition, i.e. cases of types B1–4 where the aorta receives aerated blood whether it arises from the morphological left ventricle or from the right. This is the most common use of the term and is of value from a clinical standpoint, as this small group of cases has a considerably better prognosis than other types of complete transposition.

Illustrative Case Report

Clinical Features. A girl, aged 3 $^1/_2$ months was admitted to hospital moribund, with a "slow pulse rate." Death occurred twenty minutes later. There had been two cyanotic attacks earlier in the day. Delivery had occurred normally at full term but during pregnancy the fœtal heart rate had been abnormally slow. Examination after birth revealed slight cyanosis, moderate cardiac enlargement, and an apical systolic murmur. The pulse rate was 48 and an electrocardiogram showed 2:1 A-V block. Feeding had been difficult and occasional attacks of cyanosis and dyspnœa had occurred.

Post-mortem Examination. A complete necropsy was performed 20 hours after death. The body was that of a poorly developed girl of 61 cm. length, with moderate cyanosis but no œdema. The only significant findings outside the cardiovascular system were generalized visceral congestion, bilateral pleural effusions of 15 ml., and a peritoneal effusion of 50 ml.

The heart (90 g.) was much enlarged and lay in the left thorax with its long axis directed downwards and to the left. It was roughly triangular in outline with a prominence at the left upper portion of the anterior surface from which the large aorta arose. The pulmonary artery lay posterior to, and to the right of, the aorta. Both vessels coursed directly upwards. The right atrium was large and projected to some extent to the left in front of the great vessels. The small elongated left atrium lay behind the great vessels and its tip just extended to the left of the aorta.

The right atrium received the superior and inferior venæ cavæ and the coronary sinus but the venous valves were rudimentary. The fossa ovalis measured 1·3 × 1·0 cm. and showed a valvular defect measuring 0·7 × 0·3 cm.

The ventricle that lay on the right side (Fig. 2a) resembled a mirror image of a morphological left ventricle. The maximum internal diameters were 4·5 cm. vertically and 2·8 cm. transversely. The wall was 0·8 cm. thick. The atrio-ventricular orifice measured 4·9 cm. in circumference and bore two cusps situated anteromedially and posterolaterally. The chordæ tendineæ of the cusps arose from two large papillary muscles, one anterior and one posterior. The interior of the ventricle showed a fine trabeculation. The upper part of the septum was smooth and showed three defects. One rounded defect A, 0·8 cm. in diameter, lay in the midpart beneath the septal cusp of the pulmonary valve; its walls were muscular and rounded save posteriorly where it was membranous and the medial portions of the atrio-ventricular valves were fused together: the upper part of the septum posterior to this defect was membranous. Two defects B and C, of 0·9 and 0·2 cm. diameter respectively, with rounded muscular walls were present in the most anterior part of the septum.

The pulmonary artery arose from the midpoint of the ventricle that lay on the right side. At its origin it measured 2·2 cm. in circumference. It lay over and behind the septal defect A and anterior to the anterior leaf of the right atrio-ventricular valve. The pulmonary valve possessed two cusps, left and right, of about equal size. The right cusp bore the same intimate relation to the anterior cusp of the right atrio-ventricular valve as the left posterior cusp of a normal aorta does to the anterior cusp of the mitral valve.

The left atrium was slightly smaller than the right atrium. It received four pulmonary veins in a normal manner and showed the small opening of the foramen ovale.

The ventricle that lay on the left side (Fig. 2b) resembled a mirror image of a morphological right ventricle. Its maximum internal measurements were 3·8 cm. vertically and 2·2 cm. transversely. Its wall was 0·7 cm. thick. The atrio-ventricular orifice was 3·7 cm. in circumference and possessed medial, posterior, and antero-lateral cusps. The anterior papillary muscle was slender, bifid, and inserted half way up the ventricular wall. The posterior papillary muscle arose somewhat laterally from the inferior part of the ventricle. The medial cusp was attached by numerous chordæ to the upper portion of a muscular

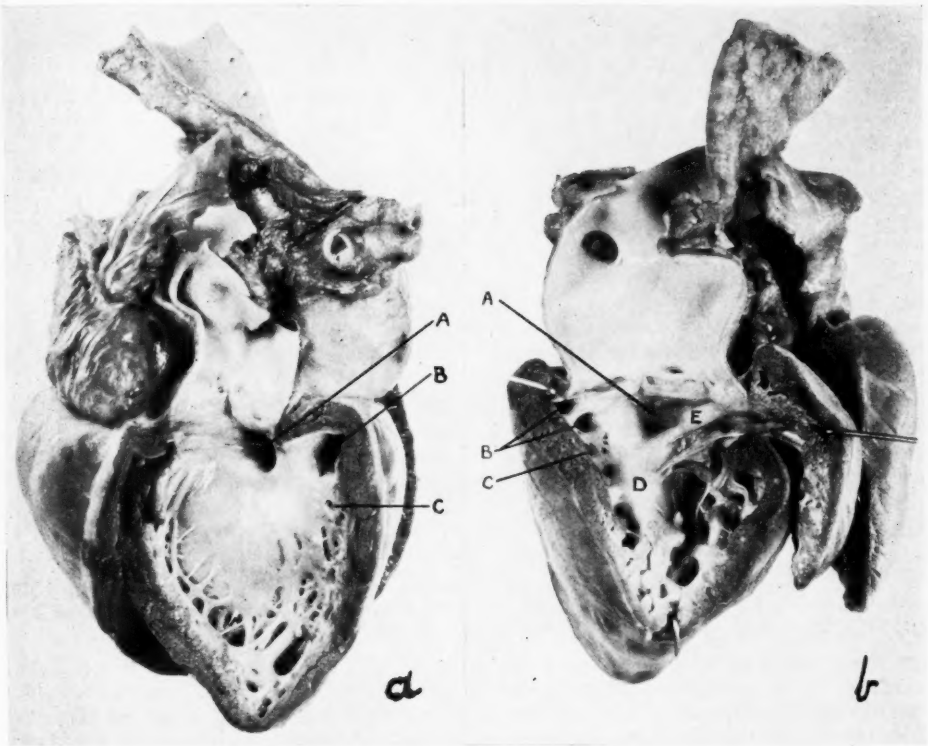

FIG. 2.—Septal aspect of ventricle which lay on (a) the right side (morphological left ventricle), and (b) the left side (morphological right ventricle). A, B, and C=ventricular septal defects. D=crista supraventricularis. E=bulbo-atrial ledge.

band, D (described later), and adjacent ventricle. The posterior cusp was attached by chordæ to the posterior papillary muscle and adjacent ventricle. The antero-lateral cusp was attached by chordæ to the two papillary muscles and the muscular bands D and E. The surface of the ventricular septum was irregular and heavily trabeculated and in its upper portion there were the three defects corresponding to those seen on the right side of the septum. The defect A was centrally situated beneath the posterior cusp of the aortic valve. The large anterior defect B was subdivided by a smooth muscular band and just below it was the smaller defect C. A firm muscle band D arose on the anterior wall of the ventricle close to the apex below the anterior papillary muscle. It coursed to and became incorporated with the septum, and minor bands from the ventricular wall joined it including one from the base of the posterior papillary muscle. The band had a slightly concave anterior margin. It ascended on the left side of the septum and attained a maximum width of 1·0 cm. just below the septal defect A where it divided. The larger part then ascended to the posterior half of the right anterior aortic cusp and its junction with the posterior cusp. The smaller part formed the inferior border of the septal defect A. Anterior to the main band there was a deep recess into which septal defects B and C opened. This band D was interpreted as the crista supraventricularis and it divided the ventricle into a sinus portion (inflow tract) and a conus portion (outflow tract). There was another small muscle band E which arose from the inferior border of the septal defect A, where it was attached by a fibrous septum to the posterior membranous part of the ventricular septum. It arched over the roof of the ventricle between the aorta and the anterior tricuspid leaflet to become incorporated in the upper part of the antero-lateral wall of the ventricle. This band E was interpreted as the bulbo-atrial ledge.

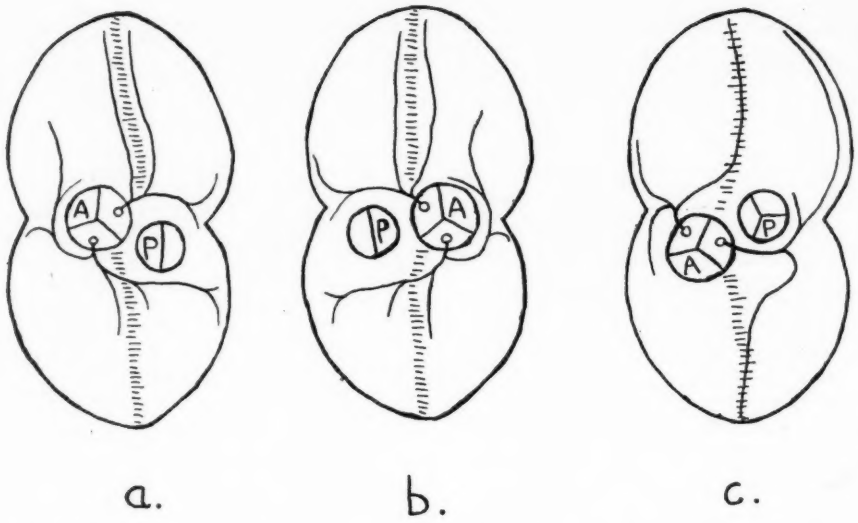

FIG. 3.—Diagram illustrating the course of the coronary arteries in this case (a), its mirror image (b), and the normal distribution (c). The heart is depicted, viewed from above, as though it were sectioned coronally from the apex to the base and opened with the anterior surface above and the posterior surface below. A indicates the aorta; P, the pulmonary artery. The shaded areas denote the septa present (after Harris and Farber).

The aorta arose from the most anterior part of the ventricle on the left side. It did not have the usual close relationship to the left atrio-ventricular orifice, being separated from it by the muscle bands D and E. At its origin the aorta measured 3·9 cm. in circumference and possessed a posterior and left and right anterior cusps. The coronary artery distribution is shown in Fig. 3a. The right coronary artery arose from the right anterior sinus and immediately gave off two large anterior descending branches which coursed on either side of the septum. It continued in the right atrio-ventricular groove giving off several small branches. The left artery arose from the posterior sinus and immediately gave off a large branch which coursed round the left side of the base of the aorta to supply branches to the lateral and anterior wall of the left-sided ventricle. The main stem coursed to the right giving off branches to the posterior septum and the posterior and lateral walls of the right-sided ventricle.

The ductus arteriosus was patent with a lumen of 0·2 cm. diameter. The remaining branches of both aorta and pulmonary artery were normal.

DISCUSSION

This case shows situs solitus of the sino-atrial portion of the heart, which is of normal structure, and of all other viscera. The ventricles, however, are inverted and they form a mirror image not of normal ventricles but of those found in complete transposition of the great vessels (crossed transposition or type 3 of Spitzer). The great vessels show complete transposition as evidenced by their almost parallel upward course, their origin one from each ventricle, the anterior position of the aorta, and the internal structure of the ventricles. In addition the bulbus is inverted as shown by the left anterior position of the aorta and the right posterior position of the pulmonary artery. Furthermore, the distribution of the coronary arteries shows transposition and inversion. This is illustrated diagrammatically in Fig. 3 which shows (a) the coronary distribution in this case, (b) its mirror image, and (c) the normal distribution. Comparing the mirror image of this case with the normal distribution, the left circumflex and anterior descending arteries take origin from the left anterior aortic sinus which was originally in the right anterior position, and the right

circumflex and posterior descending arteries take origin from the posterior aortic sinus which was originally in the left anterior position.

This case therefore presents inversion of the bulbo-ventricular loop coupled with complete transposition of the great vessels and is an example of corrected transposition.

Twenty-four cases of corrected transposition have been recorded. Six are of type B1, complete transposition with bulbus inversion (Grunmach, 1890; Theremin, Case 47, 1895; Lewis and Abbott, 1915; Doerr, Case 1, 1938; Carns *et al.*, 1941; and Brown, 1950). Two cases are of type B2, complete transposition with sino-atrial and ventricular inversion (Gutwasser, 1870; and Fingerhuth, 1901). Fifteen cases are of type B3, complete transposition with bulbo-ventricular inversion (Rokitansky, p. 83, 2 cases, 1875; Tönnies, 1884; Mann, 1889; Lochte, 1894; Theremin, Case 46, 1895; Peters, 1901; Sato, 1914; Wurm, 1927; Stejfa, 1931; Walmsley, 1931; Roos, 1936; Harris and Farber, Case 16, 1939; Liebow and McFarland, Case 1, 1941; Lev, Case 3, 1954). One case is of type B4, complete transposition with sino-atrial inversion (Graanboom, 1891). Some other cases are unacceptable on account of associated lesions such as certain anomalies of the great veins or a common atrio-ventricular valve which impair the functional correction. (Geipel, 1903; Schmincke and Doerr, 1939; Moscovitz *et al.*, 1952).

Analysis of the recorded cases reveals several points of interest even though some of the reports are incomplete. The sexes are equally represented, 10 males and 11 females. The length of life is variable ranging from 9 days to 46 years with an average of 14 years. The outlook, therefore, is poor, though better than in ordinary complete transposition for which Abbott (1936) gives mean survival times of six months with an intact ventricular septum and three years with a defective ventricular septum. The main reason for this poor prognosis is the frequent existence of associated anomalies. Of 18 cases in which the information is given, only two were without other structural cardiac abnormalities and one of these had complete heart block. Septal defects (atrial or ventricular or both) were especially common, and in only four cases were both septa intact. This is not unexpected in view of the abnormal mechanism of septum formation in cases showing inversion and transposition. The septal defects varied considerably in size and some ventricular septal defects were large. Somewhat surprisingly most of the cases with large ventricular septal defects lived considerably longer than the mean for cases of corrected transposition. Of particular interest are the anterior septal defects in Wurm's case and the present case and the anterior septal niche in the case of Liebow and McFarland. According to Spitzer the posterior border of this defect or niche represents the forward directed course of the ventricular continuation of the crista aortico-pulmonalis, thus confirming that the anterior part of the ventricular septum in these cases is derived from the crista supraventricularis.

Another feature of these cases which is probably related to the abnormal septation of the heart is that five cases had heart block, complete in three, 2:1 A-V block in one, and right bundle-branch block in one.

Finally, in eight cases the coronary artery distribution showed inversion and transposition thus supporting the hypothesis that the cases are to be regarded as forms of inverse transposition. That other mechanisms may account for some cases is suggested by the finding that in two cases the coronary artery distribution showed only inversion.

SUMMARY

The concept of corrected transposition of the great vessels is discussed and it is suggested that the use of the term should be restricted to cases of functionally corrected complete transposition.

A case of corrected transposition is reported and compared with previously recorded cases.

Corrected transposition is a rare anomaly. It is commonly associated with other congenital heart lesions and although the prognosis is poor it is much better than in the usual forms of complete transposition. The genesis of the lesion remains obscure but it appears to involve both transposition and inversion of various parts of the cardiac tube.

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AUSCULTATORY AND PHONOCARDIOGRAPHIC SIGNS OF ATRIAL SEPTAL DEFECT

BY

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Atrial septal defect from persistence of the ostium secundum, or occasionally of the ostium primum, is one of the most common varieties of congenital heart disease. The clinical signs in previously published cases were evaluated by Roesler (1934), and clarified in a large personal series by Bedford *et al.* (1941). At that time the frequency of a systolic murmur was well recognized: it had been attributed by Roesler (1934) to associated mitral valve disease, and by Taussig *et al.* (1938) to interatrial flow. Diastolic murmurs were ascribed to mitral valve disease or to pulmonary incompetence. The pulmonary second sound was described as accentuated. The diagnosis rested mainly on the radiological findings first described by Assman (1929), and the electrocardiogram (Routier *et al.*, 1940). Physical examination, except for the evidence of right heart involvement, was thought to offer little or no assistance in the diagnosis of atrial septal defect (Burrett and White, 1945). Cardiac catheterization enabled the diagnosis to be made at an earlier stage (Brannon *et al.*, 1945) and the physical signs were re-examined by Barber *et al.* (1950), and by Wood (1950) who pointed out that the second sound was split and not accentuated in uncomplicated atrial septal defect. They found a diastolic murmur at the left sternal edge in half their cases and attributed this to pulmonary incompetence. The development of the phonocardiograph has allowed a more accurate analysis of the heart sounds and murmurs in atrial septal defect. This shows that auscultation can be an important aid to the clinical diagnosis.

Method of Investigation

An auscultatory and phonocardiographic investigation was made of 40 consecutive patients in whom the diagnosis of atrial septal defect as the main cardiac abnormality was established by cardiac catheterization. There were three main groups (Table I). In 23 patients it was thought to be uncomplicated and a left-to-right shunt of 3 to 14 litres a minute was found. In 6 of these patients a small pressure gradient

TABLE I

Atrial Septal Defect

	Catheterized	Operation and/or necropsy	Total
Uncomplicated	23	3	26
Additional pulmonary stenosis	7	1	8
With pulmonary hypertension	10	6*	16
Total	40	10	50

* 2 with mitral stenosis.

(less than 15 mm. Hg) was found across the pulmonary valve and was thought to be related to the high flow and dilated pulmonary artery rather than to additional pulmonary stenosis. In a second group of seven cases a pressure gradient of 25 to 50 mm. Hg was found across the pulmonary valve and was attributed to additional pulmonary stenosis—a substantial left-to-right shunt being maintained in all these patients. Patients with severe pulmonary stenosis were not included. In a third group of 10 patients there was pulmonary hypertension (pulmonary artery pressure greater than 50 mm. Hg) with raised pulmonary resistance.

An additional 10 patients with atrial septal defect were studied in whom operation or necropsy was performed providing exact anatomical diagnosis particularly in relation to the mitral valve. The mitral valve was specially examined in a further 7 post-mortem cases in whom no investigations had been possible.

Auscultation was carried out in each case and the intensity of every sound and murmur was graded—the classification of Freeman and Levine (1933) being used for systolic murmurs. Special attention was paid to the second heart sound throughout the respiratory cycle and to the timing of systolic and diastolic murmurs. These signs were correlated with the electrocardiogram, radiogram, and results of cardiac catheterization.

High-frequency phonocardiograms (Leatham, 1952) were taken by one of us in each of the 50 cases,

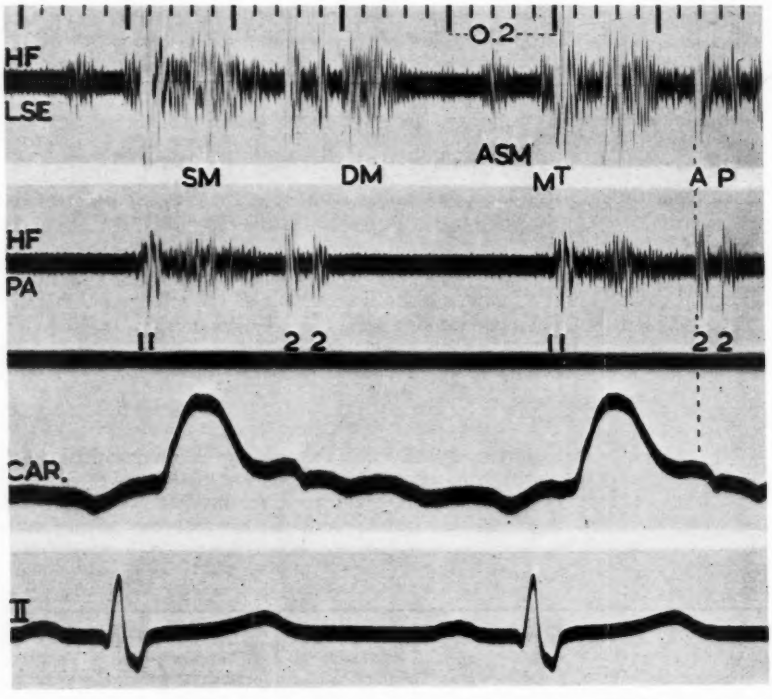

FIG. 1.—Atrial septal defect (PA P. 20/3 mm. Hg. Pulmonary flow 16 l./min., systemic 5 l./min.). Simultaneous high-frequency phonocardiograms (HF) from the lower left sternal edge (LSE) and pulmonary area (PA) with indirect carotid pulse (CAR) and electrocardiogram (II). Splitting of first sound with accentuation of second, tricuspid (T), component (coinciding with carotid upstroke—delay 0·04 sec.—and therefore too late for mitral closure). Splitting of second sound with aortic component (A) preceding pulmonary component (P) by 0·06 sec. Ejection mid-systolic murmur (SM). Delayed diastolic murmur (DM) beginning 0·05 sec. after onset of P2. Right atrial systolic murmur (ASM) 0·08 sec. after onset of P wave. Time intervals in this and subsequent records are 0·20 and 0·04 sec.

including the 10 with operative or necropsy control, and were repeated in three after surgical repair. Simultaneous records from different areas with indirect carotid and jugular tracings and electrocardiogram were made in all cases and, in 6, phonocardiograms were recorded at the same time as the pressure pulses during cardiac catheterization. The mitral valve component of the first sound was identified by its dominance at the mitral area and its relation to the upstroke of the carotid pulse, and the tricuspid component by its dominance at the left sternal edge and its relation to the right ventricular pressure pulse. The aortic component of the second sound was identified by its relation to the dicrotic notch of the carotid tracing (Fig. 1), and the pulmonary component from its dominance in the pulmonary area and its relation to the dicrotic notch of the tracing from the pulmonary artery (Fig. 2). The interval from the onset of QRS to the beginning of the upstroke of the right ventricular pressure pulse was measured in all patients, and to the upstroke

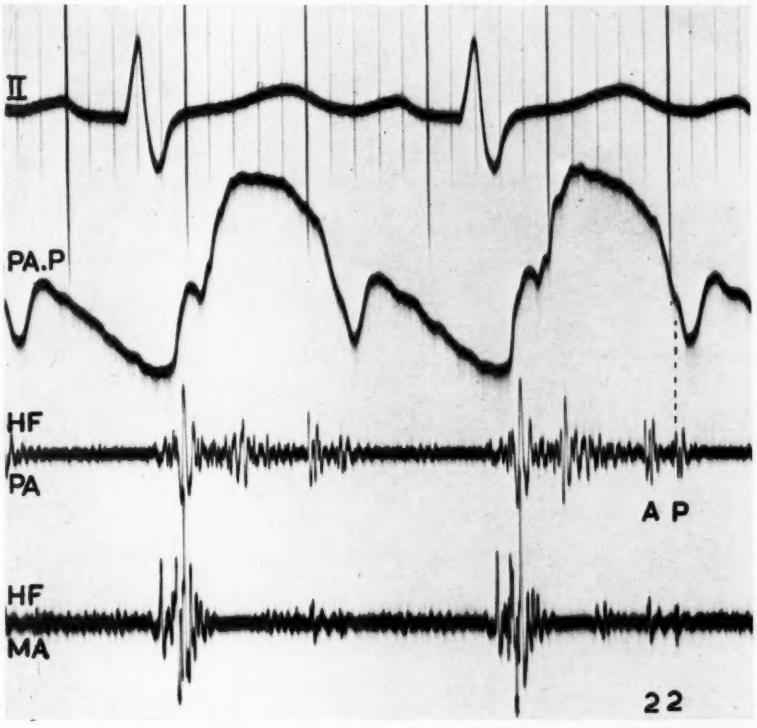

FIG. 2.—Atrial septal defect (same case as Fig. 1). Simultaneous pressure pulse from pulmonary artery (PA P) and phonocardiograms from pulmonary and mitral (MA) areas. The later component of the second sound is shown to be pulmonary by its relation to the dicrotic notch of the PA pulse (delay 0·03 sec.).

of the left ventricular pressure pulse in ten, with an allowance of 0·02 sec. for delay in the catheter (Leatham and Vogelpoel, 1954). Delay in pulse wave transmission from the aortic valve to the carotid artery was assumed to be given by the time interval from the onset of the aortic component of the second sound to the nadir of the dicrotic notch of the indirect carotid tracing. The duration of right and left ventricular systole was estimated by the time interval between tricuspid and pulmonary, and mitral and aortic valve closures, respectively.

RESULTS

First Heart Sound. Splitting of the first sound was recorded in 24 cases yet it was seldom a striking physical sign on auscultation except in the six cases with complete right bundle-branch

block (Fig. 11). In 18 of the 24 cases in which the phonocardiogram showed splitting, identification of each component was possible and mitral closure invariably preceded tricuspid closure, as in normal subjects (Leatham, 1954). In two patients with complete right bundle-branch block and wide splitting of the first sound in whom pressure pulses were obtained from both ventricles, the first component was proved to be mitral by its synchrony with left ventricular upstroke, and the second to be tricuspid by its synchrony with a delayed right ventricular upstroke. In patients with pulmonary hypertension the first sound was usually single. The first sound was judged to

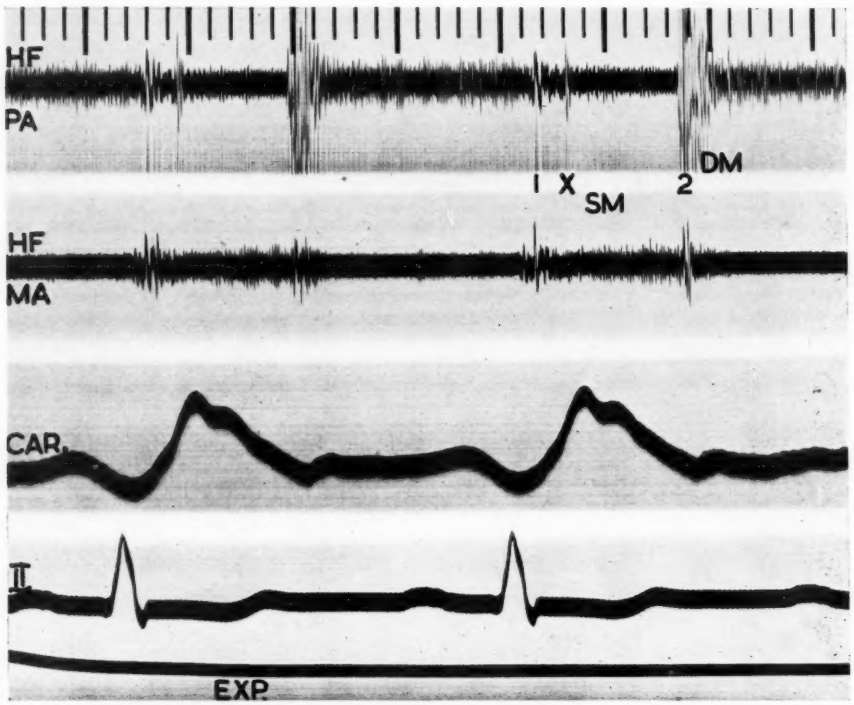

FIG. 3.—Atrial septal defect with pulmonary hypertension (RV P, 135/5 mm. Hg) and reversed shunt. (Pulmonary flow 3·6 l./min, systemic flow 4·3 l./min.) Ejection sound (X) 0·06 sec. after onset of first sound recorded in expiration (EXP.). Large single second sound immediately followed by long early diastolic murmur due to pulmonary incompetence. Pansystolic murmur at mitral area.

be increased in intensity in 17 patients. When the first sound was split in these patients neither component was constantly responsible for the increase in intensity, but in several patients with high rates of pulmonary flow the later tricuspid component was strikingly accentuated (Fig. 1).

A pulmonary early systolic ejection sound was recorded in 15 patients (Fig. 3) and was associated with pulmonary hypertension in 8, and with additional pulmonary stenosis in 2. This extra sound was clearly audible in 11 of the 15 patients.

The Second Heart Sound. In healthy subjects the second heart sound in the pulmonary area is single or split by less than 0·03 sec. in the expiratory phase of continuous respiration, and becomes more widely split, 0·05 sec. or more, during inspiration (Fig. 4). Wide splitting of the second heart sound in the expiratory phase of respiration, without much increase on inspiration, was

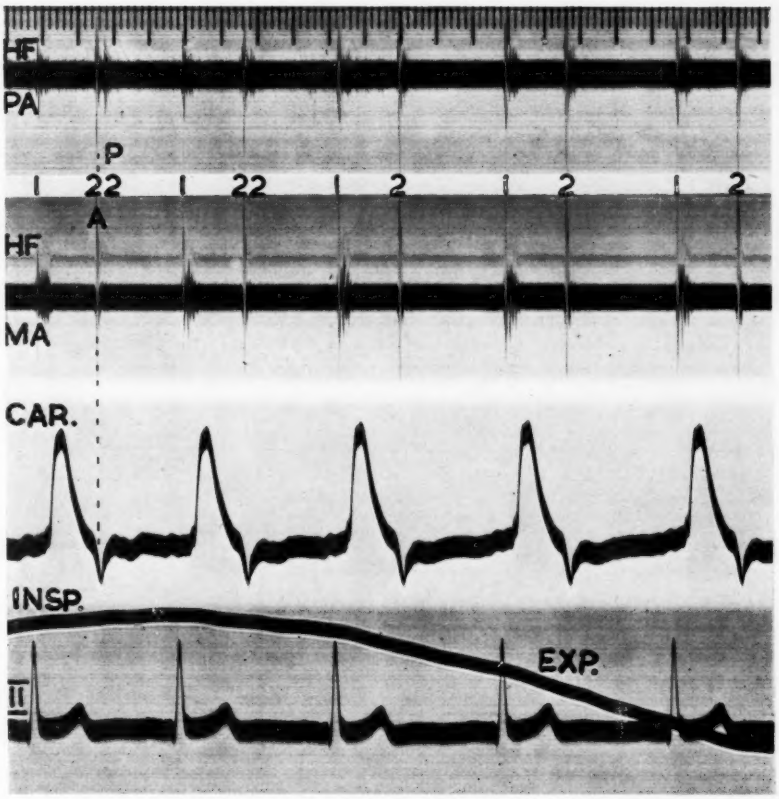

FIG. 4.—Normal subject. During inspiration the second sound in the pulmonary area is split by 0·05 sec., and becomes single in the expiratory phase of respiration. The first component is shown to be aortic by its synchrony with the dicrotic notch of the carotid tracing, and the second pulmonary by its localization to the pulmonary area.

recorded in 35 of our cases (Fig. 5) and this abnormality could almost invariably be recognized by auscultation. A satisfactory tracing throughout the respiratory cycle was obtained in 30 cases. There was no change in the width of splitting during inspiration in 21 and in the remaining 9 the split increased by an average of 0·015 sec. With synchronous phonocardiograms and carotid tracings it was found that the normal order of events was maintained—aortic valve closure before pulmonary—and that the wide split was due to relative delay in the pulmonary component (Fig. 1 and 2). In 26 cases the split in expiration was 0·03 to 0·05 sec.: in 9 cases it was wider, 0·06 to 0·10, and 6 of them were found to have additional pulmonary stenosis. Five of our 40 cases did not show this physical sign of wide and relatively constant splitting of the second heart sound, and in 2 no splitting of the second sound could be heard or recorded (Fig. 3). Both patients had very high pulmonary pressures and resistances with a reversed shunt, and showed the clinical picture of Eisenmenger's syndrome. In the other 3, one of whom had pulmonary hypertension, the splitting was slight, measuring less than 0·03 sec. in expiration.

The intensity of the two components of the second sound in the pulmonary area could not be measured directly, but their relative intensity could be compared from their size on the high-frequency

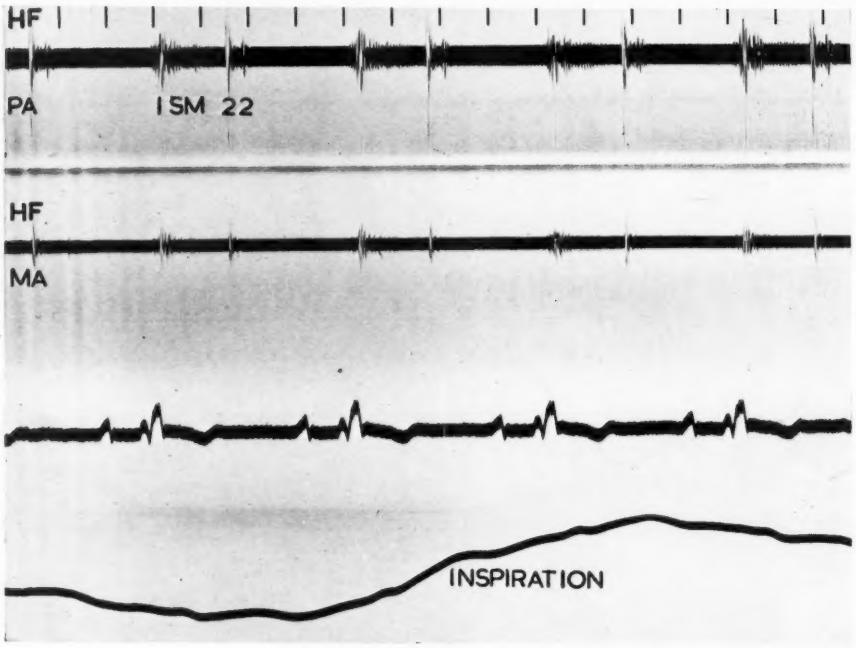

FIG. 5.—Atrial septal defect. Wide splitting of second heart sound remaining unchanged throughout the respiratory cycle.

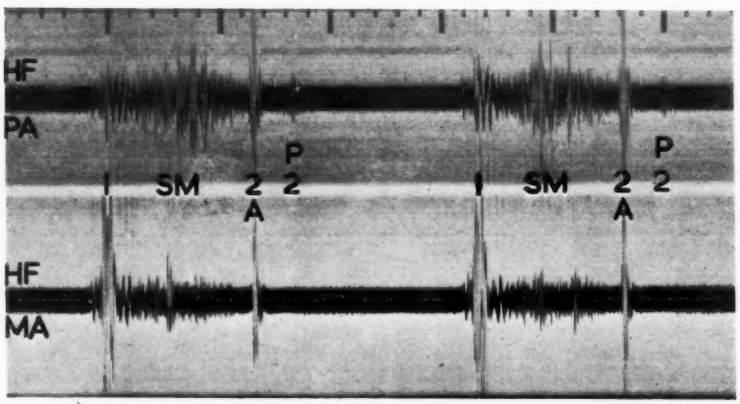

FIG. 6.—Atrial septal defect with pulmonary stenosis (pulmonary flow 19 l./min., systemic flow, 7 l./min., PA P, 18/3 mm. Hg, RV P, 48/0 mm. Hg). Pulmonary component of second sound delayed by 0·08 sec. and diminished in intensity.

phonocardiogram. In uncomplicated atrial septal defect the aortic and pulmonary components were about equal and the ratio between them was never greater than two to one (Fig. 1). With additional pulmonary stenosis the intensity of the pulmonary component was diminished in 5 out of 7 cases, the pulmonary component being reduced to as little as one-fifth of the aortic in some (Fig. 6). With pulmonary hypertension (and splitting of the second sound), the pulmonary component was increased in intensity. There was a ratio of 4 to 1 or more in most cases (Fig. 7),

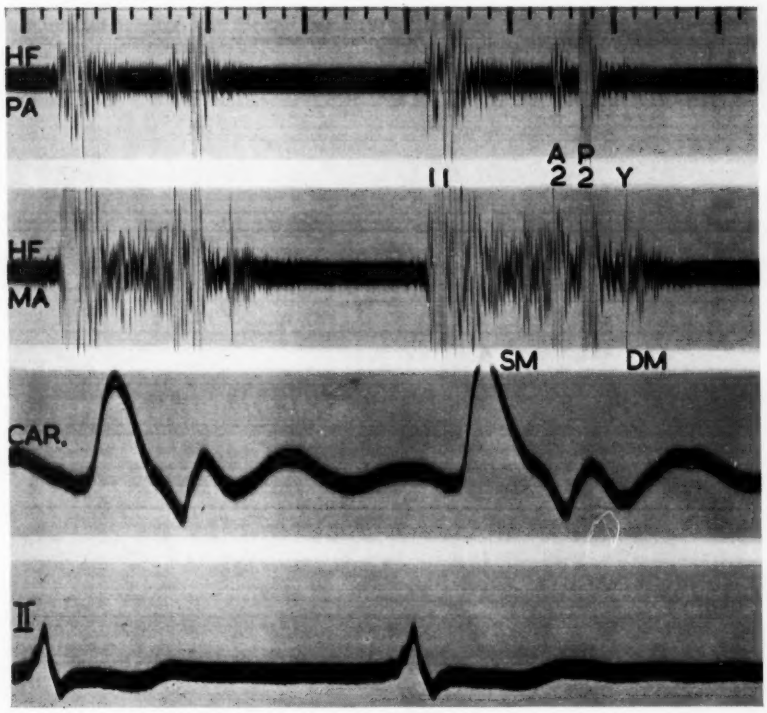

FIG. 7.—Atrial septal defect with pulmonary hypertension (PA P, 85/30 mm. Hg) and tricuspid incompetence, and maintenance of left-to-right shunt. (Pulmonary flow 10·4, systemic flow 4·5, l./min.) Wide splitting of second sound with accentuation of pulmonary component and transmission to mitral area. Early diastolic sound (Y) 0·08 sec. after P2 followed by delayed diastolic murmur. Pulmonary systolic murmur is small. Pansystolic murmur was attributed to tricuspid incompetence. No mitral disease at operation.

but it was within the normal range of 2 to 1 in one. Propagation of the pulmonary component to other areas, making splitting of the second heart sound audible at the apex, is not found in healthy subjects, and usually indicates accentuation of the pulmonary component from pulmonary hypertension (Fig. 7). Splitting of the second sound at the apex was found in all our patients with pulmonary hypertension, except the two with a single second sound in the pulmonary area, but was also present on auscultation in 7 patients with uncomplicated atrial septal defect, and on the phonocardiogram in a further 8 (Fig. 8).

Diastolic Sound. An extra sound in diastole was recorded in 10 patients (Fig. 7) and was

audible in 4 of them. This sound was high pitched and snapping, maximal at the lower left sternal edge and nearly always of very low intensity and difficult to hear. This extra sound came from 0·03 to 0·08 sec. after the onset of pulmonary valve closure in 8 patients, but in two the interval was longer, measuring 0·11 and 0·12 sec.

Systolic Murmurs. There was invariably a systolic murmur. In 36 the murmur was best heard at or near the pulmonary area and was shown on the phonocardiogram to be of a distinctive shape which could usually be appreciated clinically. It began soon after the first sound, reaching a maximum in early or mid-systole, and diminished in intensity before the second heart sound. The phonocardiogram showed that this murmur always ended before pulmonary valve closure and

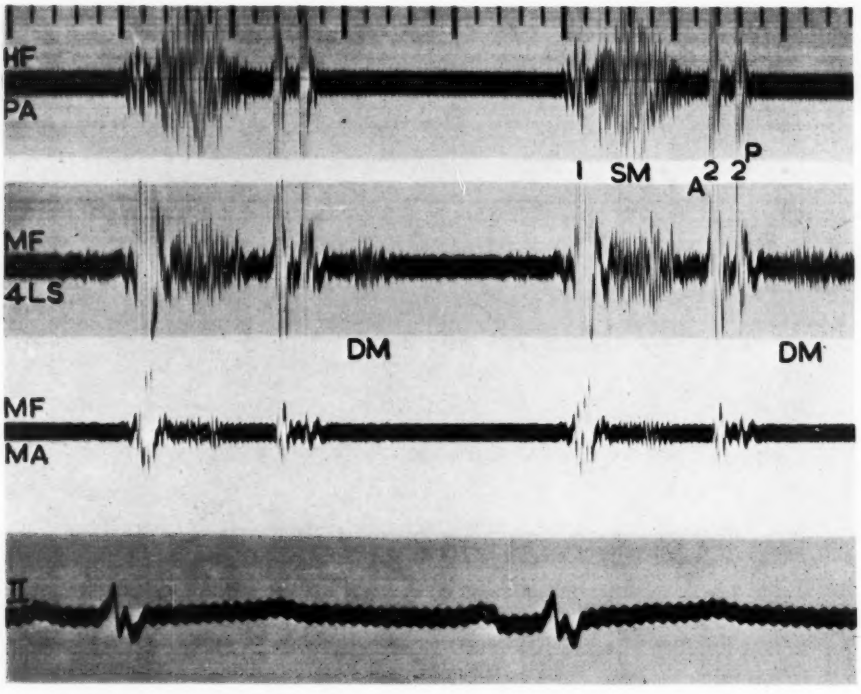

FIG. 8.—Atrial septal defect (pulmonary flow 8, systemic flow 4, l./min.; PA P, 22/6 mm. Hg). Pulmonary systolic murmur, ending before both components of second sound. P2 transmitted to apex with normal pulmonary pressure. Delayed diastolic murmur shown in medium frequency recording (MF) from the fourth space at the left sternal edge (4 LS).

in uncomplicated atrial septal defect even before the earlier aortic valve closure (Fig. 8); it tended to be slightly longer when there was additional pulmonary stenosis. The pulmonary systolic murmur was loudest in the second left intercostal space in 29 and the third or fourth space in 7 of the 36 cases. In 30 a murmur of the same pattern was heard and recorded at the apex and was thought to have been transmitted from the pulmonary area (Fig. 9). The murmur was moderately loud (grade 3 or 4) in 20 and soft (grade 1 or 2) in 9 cases. In 7 the murmur was louder (grade 5) and was accompanied by a thrill, and in four of these catheterization showed additional pulmonary stenosis with a systolic pressure gradient of 25 mm. Hg or more.

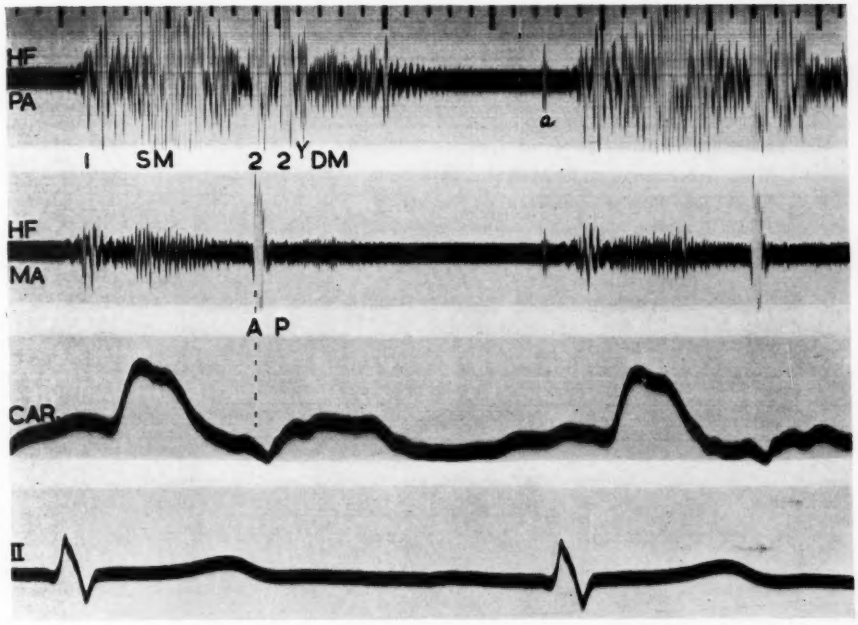

FIG. 9.—Atrial septal defect (pulmonary flow 10, systemic flow 7, l./min.; PA P, 45/10 mm. Hg). Transmission of pulmonary ejection systolic murmur to apex. Wide splitting of second sound, early diastolic sound, and delayed diastolic murmur. An artefact is marked " a ".

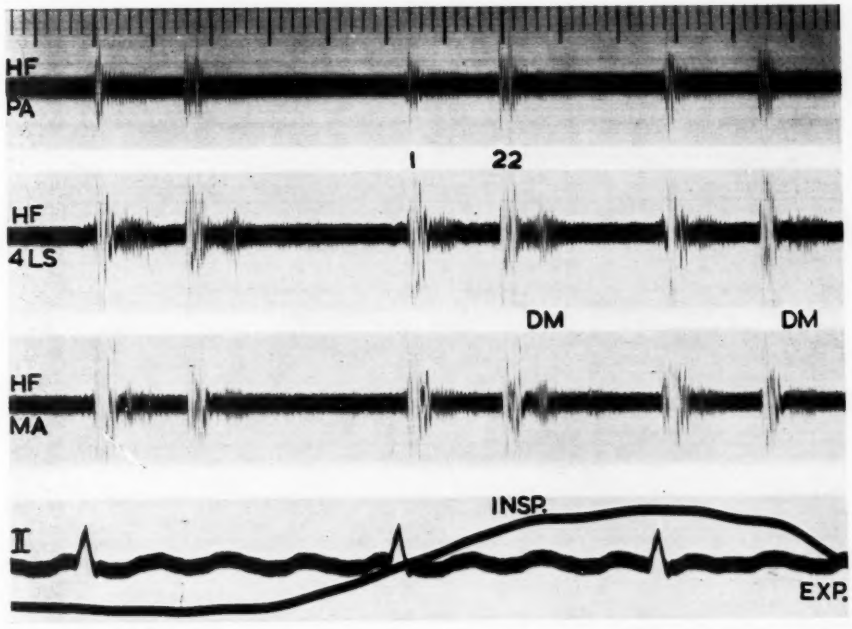

FIG. 10.—Atrial septal defect (pulmonary twice systemic flow). Delayed diastolic murmur at lower left sternal edge increasing on inspiration.

In 5 of the 40 cases a pansystolic murmur was heard and recorded from the lower left sternal edge and mitral area (Fig. 3 and 7), and was invariably associated with gross pulmonary hypertension, and in two cases with signs of tricuspid incompetence.

Diastolic Murmurs. Diastolic murmurs were heard in 27 cases and in most of them could be recorded. They were of two types. (1) In 7 a long high-pitched early diastolic murmur was heard in the pulmonary area and was thought to be due to pulmonary incompetence (Fig. 3). All these patients had pulmonary hypertension, the lowest measuring 57/30 mm. Hg, with extreme enlargement of the pulmonary artery. (2) In 21, there was a short delayed diastolic murmur maximal below the pulmonary area (Fig. 1, 7, 8, 9, and 10), often localized to the third and fourth left space or below, and near the left sternal edge. The pitch of the murmur was often considered

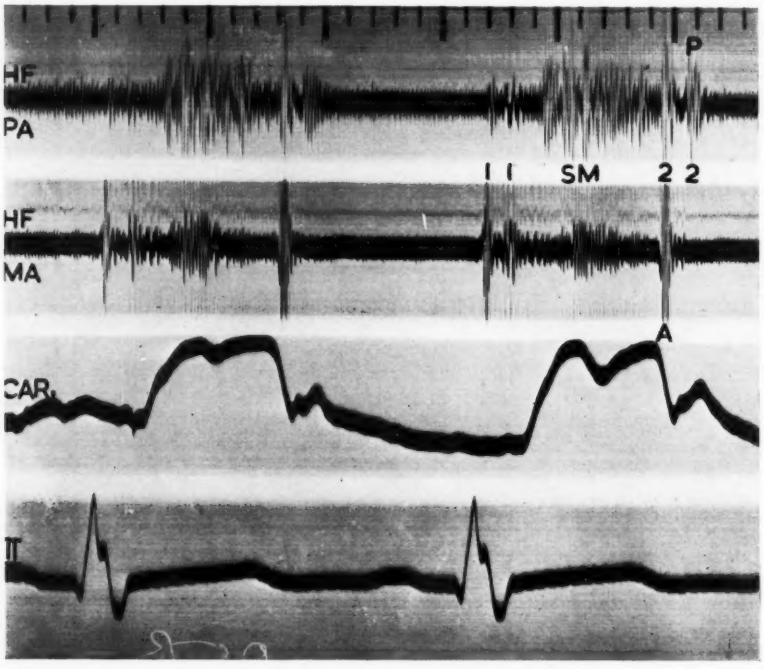

FIG. 11.—Atrial septal defect with complete right bundle-branch block. Wide splitting of first and second heart sounds.

to be intermediate between that of mitral and aortic diastolic murmurs, and the quality was frequently "scratching." Variation in intensity of the murmur was sometimes very striking, and a loud murmur might become inaudible and not able to be recorded at the next examination. There was an obvious increase in intensity of the murmur during inspiration (Fig. 10) and following exertion. In five patients the murmur followed immediately or shortly after an early diastolic sound. The delayed diastolic murmur began from 0·04 to 0·12 sec. after the onset of pulmonary valve closure, and in cases with simultaneous phonocardiograms and right auricular tracings its onset was shown to be 0·02 to 0·04 sec. after the peak of the V wave (Fig. 12). The duration of the murmur was short, varying from 0·04 to 0·20 sec.

An atrial systolic (presystolic) murmur was recorded from the apex and lower left sternal edge in 3 of our 40 patients (Fig. 1 and 13) and was of very low intensity being audible in only one.

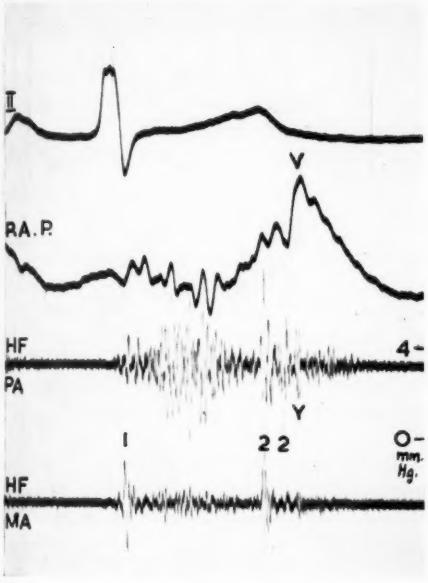

FIG. 12.—Atrial septal defect (same case as Fig. 9). Simultaneous right atrial pressure tracing (RA P) and phonocardiograms. The early diastolic sound and the onset of the delayed diastolic murmur coincide approximately with the peak of the *v* wave.

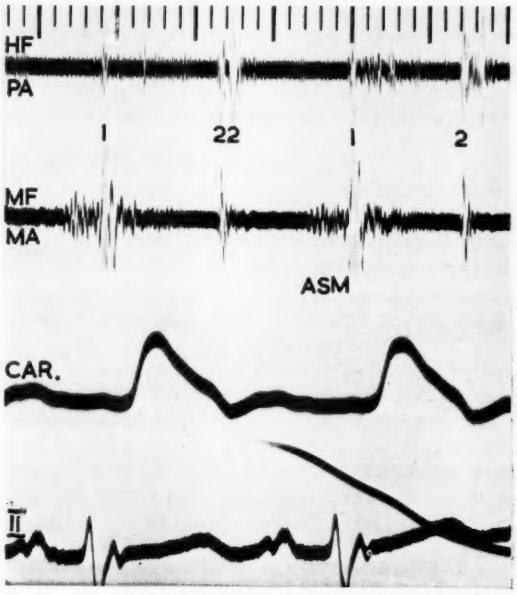

FIG. 13.—Atrial septal defect with mitral valve disease at operation. Atrial systolic vibrations begin 0·12 sec. after the onset of the P wave suggesting a left atrial origin.

DISCUSSION

The loud *first sound* in 17 patients might have been attributed to associated mitral stenosis. However, accentuation of mitral closure is not, perhaps, to be expected in mitral stenosis when there is an atrial septal defect with left-to-right shunt, as the left atrial pressure is not raised. Furthermore, added mitral stenosis was thought to be rare in our cases, as will be mentioned later, and was absent at operation in the patient with the loudest first sound that we have met. Accentuation of tricuspid valve closure was a more likely cause of the loud first sound. The increased tricuspid flow would be expected to keep the tricuspid valve open at the end of diastole causing a loud closing sound with the onset of ventricular contraction. A loud first sound was commoner in patients with high rates of flow (8 out of 13 with large shunts), but was also found in those with smaller flows (9 out of 27 with smaller shunts).

The pulmonary early systolic ejection sound and its association with enlargement of the pulmonary artery and pulmonary hypertension have been recently investigated (Leatham and Vogelpoel, 1954). It is a high-pitched sound in early systole, maximal in the pulmonary area and commonly increasing in intensity in expiration. Its location, timing, and quality can usually distinguish it from splitting of the first sound. It was recorded in 15 of our patients and was invariably associated with enlargement of the pulmonary artery. It was found in 7 of the 8 with extreme pulmonary arterial enlargement and in 8 of the 30 with slight or moderate enlargement. This sound was not confined to the patients with pulmonary hypertension though it was more frequent and more obvious in this group (8 out of 10 with pulmonary hypertension, and in 7 out of 30 with normal pulmonary pressures).

The importance of wide splitting of the *second heart sound* as a sign of atrial septal defect was pointed out by Barber *et al.* (1950) and by Matthews (1949). The phonocardiogram shows that the characteristic abnormality in atrial septal defect is the wide splitting of the second sound in the expiratory phase of continued respiration, caused by relative delay in closure of the pulmonary valve. The usual inspiratory increase is diminished or absent (Towers (1950), whose attention was drawn to this by Mr. W. Dicks). The wide and constant splitting is a particularly obvious physical sign because of the diminution of the systolic murmur before both components of the second sound.

Barber *et al.* (1950) suggested that the relative delay in closure of the pulmonary valve might be due either to delay in electrical activation of the right ventricle from right bundle-branch block, or to mechanical prolongation of right ventricular systole owing to the selective increase in right-sided flow.

A delay in activation of the right ventricle is suggested by the term " partial right bundle-branch block " (Barker and Valencia, 1949) as applied to the rSR complex of less than 0·12 sec. so frequently found in right chest leads in patients with atrial septal defect (Routier *et al.*, 1940; Barber *et al.*, 1950). Right bundle-branch block of any degree would cause delay in closure of the tricuspid valve and abnormally wide splitting of the first sound corresponding to the splitting of the second sound (Fig. 11). This was found only in the six cases with complete right bundle-branch block, and the electrical delay was confirmed in the two in whom catheterization of both ventricles was performed. The interval from the onset of QRS to the upstroke of the right ventricular pressure pulse (Q–RV) was prolonged to an average of 0·10 sec. compared with an interval of 0·05 sec. for the left ventricle (Q–LV). In the remaining 34 the cardiogram showed an rSR complex measuring less than 0·12 sec., and the first heart sound was not abnormally split. Absence of electrical delay in eight of these cases where both ventricles were catheterized was confirmed by finding a Q–RV time of 0·05 sec., which is less than the average normal given by Coblentz *et al.* (1949), and a Q–LV time approximately the same. Furthermore the presence of an rSR complex in 11 subjects with either a healthy heart or rheumatic heart disease gave rise to no abnormal splitting of the second heart sound. Thus, the widely split second sound of atrial septal defect cannot be explained by delay in electrical activation of the right ventricle in the majority of cases.

Unequal duration of right and left ventricular systole might be expected from the greatly increased right-sided flow of atrial septal defect (average ratio pulmonary to systemic flow 2·3:1). The duration of right and left ventricular systole as measured from the phonocardiogram in 20 cases showed a constant prolongation of right over left of 0·02 sec., and this persisted throughout the respiratory cycle.

It is concluded that the difference between right- and left-sided flows causes relative prolongation of right ventricular systole and that this is the major factor causing the wide and constant splitting of the second sound in atrial septal defect. This conception is supported by observations on three patients in whom surgical closure of the septal defect restored normal splitting of the second heart sound without any change in the electrocardiogram. A similar mechanism is probably responsible for the phasic splitting of the second sound in normal subjects. The delay in closure of the pulmonary valve is then limited to inspiration when the negative intra-thoracic pressure causes increased filling of the right ventricle from its large extra-thoracic venous reservoir without a similar increase on the left side.

A moderately loud basal *systolic murmur* has generally been regarded as a frequent finding in atrial septal defect (Roesler, 1934; Bedford *et al.*, 1941; Barber *et al.*, 1950). A characteristic murmur that was maximal in the neighbourhood of the pulmonary area was recorded in 36 of our cases. The onset soon after the first sound, the crescendo in early or mid-systole and, most important, the cessation of the murmur before pulmonary valve closure, all suggest that this murmur is caused by the ejection of blood into the pulmonary artery. This is supported by the timing of the ejection sound, which, when present, immediately preceded the onset of the murmur (Leatham and Vogelpoel, 1954). The gap between the first sound and the onset of the murmur tended to

be longer in the patients with pulmonary hypertension (bearing an approximate relation to the isometric time of the right ventricle).

All systolic murmurs caused by the ejection of blood through the aortic or pulmonary valve have approximately the same graphic configuration whether due to stenosis, valvular disease without stenosis, increased flow, or dilatation of the vessel beyond a normal valve. In atrial septal defect the systolic murmur seems related to the increased flow into the pulmonary artery rather than to dilatation of this vessel. With added pulmonary hypertension and the greatest enlargement of the pulmonary artery, but with relatively normal flow, the murmur tended to be diminished or even absent. The most important graphic feature of the murmur is its cessation before the corresponding second sound, as would be expected since the flow is at that time much diminished. With added pulmonary stenosis the murmur tended to last longer because of the prolongation of right ventricular systole and the greater intensity of the murmur. In atrial septal defect there was frequent transmission of the ejection systolic murmur to the apex, even when this murmur was of slight intensity. This finding may be explained by the greatly dilated right ventricle forming the apex of the heart, and is comparable with the transmission of aortic systolic murmurs to the apex when this is formed by the left ventricle. The systolic murmur occasionally had the superficial scratching quality not uncommonly found in other pulmonary systolic murmurs in the absence of pulmonary stenosis.

In 5 patients quite a different systolic murmur was recorded. The murmur was pansystolic, its intensity being almost constant throughout systole extending up to the second sound. This suggested that it was due to regurgitation from ventricle to atrium where the pressure difference, and therefore flow, continues right up to and even beyond aortic and pulmonary valve closure. This murmur was equally loud at the tricuspid and mitral areas and it was difficult to decide its source. All 5 had extreme pulmonary hypertension and were therefore liable to a functional tricuspid incompetence. In two the venous pulse showed obvious systolic waves and in one of them the systolic murmur became louder during inspiration. It was difficult to exclude organic mitral incompetence as the cause of the murmur in the other three; indeed, one of them came to necropsy and had additional mitral valve disease.

The *diastolic murmurs* in patients with atrial septal defect have been attributed to pulmonary incompetence or to coincident mitral valve disease. A long high-pitched diastolic murmur beginning immediately after pulmonary valve closure, and maximal in the pulmonary area, was found in 7 of our patients and was invariably associated with great enlargement of the pulmonary artery and unmistakable signs of pulmonary hypertension. This murmur was attributed to pulmonary incompetence and resembled in every way the early diastolic murmur found in pulmonary hypertension from other causes.

A different short diastolic murmur was found in 21 of our patients and has been noted by Evans (1954), and Reinhold and Nadas (1954). It started appreciably later than pulmonary valve closure and corresponded with the period of rapid ventricular filling. There seem to be three possible causes for this murmur—coincident mitral valve disease, flow through the atrial septal defect, or increased flow through a normal tricuspid valve.

An abnormal mitral valve is frequently associated with atrial septal defect (41 of Roesler's (1934) cases and 8 of our 17 with necropsy or operative confirmation), although frank stenosis is much less common (Nadas and Alimurung, 1952), occurring in only 6 of Roesler's cases and 2 of ours. Associated mitral valve disease has usually been held responsible for the delayed diastolic murmur in atrial septal defect. The site, quality, and increase in intensity on inspiration all suggested that this diastolic murmur was not of mitral origin. It was therefore likely to be associated with the shunt through the atrial septal defect or the increased flow through the tricuspid valve. The presence of the diastolic murmur in only 2 of the 10 cases with pulmonary hypertension and reduced left-to-right shunt is in keeping with either of these two possibilities. Thus, the clinical evidence suggested that this diastolic murmur was not related to mitral valve disease. Wood (1955) mentions a case of atrial septal defect in which a loud delayed diastolic murmur with thrill

led to the diagnosis of added mitral stenosis, but at operation the mitral valve was normal. We have heard and recorded loud delayed diastolic murmurs in three patients with atrial septal defect who had normal mitral valves at necropsy or operation, and there was no diastolic murmur in two others with atrial septal defect and appreciable mitral stenosis.

The location of the delayed diastolic murmur about the fourth intercostal space and near the sternum would be consistent with its origin from flow through either the atrial septal defect or the tricuspid valve. The onset of the murmur corresponding with the descending limb of the right atrial *v* wave (Fig. 12) showed that there was a relation to the phase of maximal flow through the tricuspid valve. At this point in the cardiac cycle pressure differences between the two atria are said to be minimal (Calazel *et al.*, 1951; Schaffer *et al.*, 1954) so that a surge of flow through the defect giving rise to a murmur would not be expected. An increase in intensity during inspiration is a known feature of tricuspid murmurs and is caused by the negative intra-thoracic pressure drawing blood from the extra-thoracic systemic venous reservoir. No increase in intensity on inspiration would be expected if the murmur arose at the atrial septal defect since both right and left atria and pulmonary veins are equally influenced by the change of intra-thoracic pressure. Thus, increased flow through the tricuspid valve seems the most likely cause of the delayed diastolic murmur of atrial septal defect. The murmur is comparable with the delayed diastolic murmur from increased left-sided flow through the mitral valve in patients with ventricular septal defect and patent ductus arteriosus (Wood, 1950).

The extra diastolic sound was seldom an obvious physical sign although in one patient it was loud and had been diagnosed as the opening snap of mitral stenosis: at operation the mitral valve was normal. The sound immediately preceded the diastolic murmur, when both were present, suggesting that it might be associated with opening of the tricuspid valve—a tricuspid snap. A simultaneous recording of the right atrial pressure pulse with phonocardiograms in one case supported this possibility since the peak of *v* coincided with the extra sound (Fig. 12). The high-pitched quality of the sound and its early timing made it unlikely to be a right ventricular third heart sound.

An atrial systolic murmur was relatively uncommon in our 40 cases, but had been found in 4 of the 10 that came to necropsy or operation; 2 of them had complicating mitral valve disease. The time interval between the onset of the P wave and the atrial vibrations on the phonocardiogram was 0·09 sec. in the 2 uncomplicated cases, corresponding with the electro-mechanical interval for the right atrium measured by Coblentz *et al.* (1949). In the two patients with mitral valve disease this interval was longer, 0·12 and 0·13 sec., suggesting an origin from the left atrium, for this is known to contract later than the right (Fig. 13). A similar, though rather longer, time interval of 0·14–0·16 sec. was found in 10 cases of uncomplicated mitral stenosis. Thus, it seems that the earlier (right) atrial systolic murmur is tricuspid in origin like the delayed diastolic murmur. The later (left) atrial systolic murmur was associated with additional mitral valve disease in the only two cases in which it was found.

Added Pulmonary Stenosis, Pulmonary Hypertension, or Mitral Stenosis

The signs of atrial septal defect are modified by additional pulmonary stenosis and pulmonary hypertension. In 7 patients a systolic pressure gradient of 25–50 mm. Hg across the pulmonary valve led to the diagnosis of additional *pulmonary valve stenosis*, but atrial septal defect was still regarded as the dominant abnormality. The pulmonary systolic murmur was loud and accompanied by a thrill in 4 of these 7 immediately suggesting the additional lesion, but these signs occasionally occurred in pure atrial septal defect (3 of 33 cases). In 5 of the 7, the systolic murmur was longer than is usual in pure atrial septal defect reflecting the relative prolongation of right ventricular systole and the increased intensity of the systolic vibrations. Delay in pulmonary valve closure greater than in pure atrial septal defect, causing a split second sound of 0·06 sec. or more, was found in 6 of the 7 cases. The relative intensity of the pulmonary component was generally, but not invariably, diminished.

In 10 patients additional *pulmonary hypertension* was diagnosed, because the pulmonary artery systolic pressure exceeded 50 mm. Hg and the pulmonary resistance was greater than normal. In 8 of these, there was evidence of some right-to-left shunt since the arterial oxygen saturation was less than 90 per cent (greater than 90 per cent in our uncomplicated cases of atrial septal defect), and of these cases 2 with extremely high pulmonary resistance (22 and 25 units) had obvious central cyanosis and clubbing, and were diagnosed as Eisenmenger's syndrome (Wood, 1950). Despite the pulmonary hypertension the usual left-to-right shunt (pulmonary flow twice or more systemic flow) was maintained in all but the Eisenmenger patients and two others in whom the pulmonary resistance was almost as high.

In 8 of our 10 cases a pulmonary early systolic ejection sound was recorded, and was audible in most of them, but this sound did not invariably indicate pulmonary hypertension because it was found in 5 of our 23 uncomplicated cases. The time interval between the onset of tricuspid valve closure and the ejection sound averaged 0·06 sec. in those with pulmonary hypertension, against 0·04 sec. in the others, from the slight prolongation of isometric time in hypertension (Wiggers, 1952).

The usual ejection systolic murmur was absent in 4 of the 10 cases with pulmonary hypertension reflecting the smaller pulmonary flow in this group. The pansystolic murmur (5 cases) that was attributed to tricuspid (or mitral) incompetence was confined to this group. The pulmonary component of the second sound was invariably increased in intensity and transmitted to the mitral area. A wide and fixed splitting of the second sound was heard in 8 cases while in 2 there was a loud single second sound: these were the 2 diagnosed as Eisenmenger's syndrome, and it was concluded that absence of splitting of the second sound in the cases with pulmonary hypertension indicated balancing or reversal of the shunt. The early diastolic murmur was common (7 of the 10 cases) and was confined to this group. The delayed diastolic murmur of increased tricuspid flow was found in only 2 of these cases.

The diagnosis of additional *mitral stenosis* in cases of atrial septal defect is well known to be difficult although the incidence of significant narrowing of the mitral valve is now thought to be low and was only present in 2 of our 17 cases that came to operation or necropsy. In the absence of increased left atrial pressure the characteristic auscultatory signs such as the loud first sound, opening snap, and mitral diastolic murmur, and the selective enlargement of the left atrium do not occur. In addition the delayed diastolic murmur of atrial septal defect creates further difficulty. Our findings suggest that a left atrial systolic murmur may sometimes be of value, but often, perhaps, in the majority, the mitral stenosis is silent.

SUMMARY

The auscultatory and phonocardiographic signs are described in 50 patients with atrial septal defect and they are attributed to the increased flow through the tricuspid and pulmonary valves from the left-to-right shunt. The increased tricuspid flow frequently gives rise to a loud first sound, a delayed diastolic murmur sometimes preceded by a small sound, and occasionally a right atrial systolic murmur. The increased pulmonary flow causes a mid-systolic ejection murmur and delay in closure of the pulmonary valve giving a wide and constant splitting of the second heart sound.

With added pulmonary hypertension there is usually a pulmonary early systolic ejection sound, accentuation of the pulmonary component of the second sound, and the early diastolic murmur of pulmonary incompetence. There may be a pansystolic murmur from added tricuspid incompetence. In the presence of a high pulmonary vascular resistance, and diminution and reversal of the shunt, the tricuspid diastolic murmur, the pulmonary systolic murmur, and the wide splitting of the second sound, tend to disappear.

When pulmonary stenosis is added the systolic murmur is louder and longer and pulmonary valve closure is more delayed.

Additional mitral stenosis is difficult to diagnose since the loud first sound and the delayed

diastolic murmur preceded by an opening sound can occur in uncomplicated atrial septal defect, but it may be suspected if a left atrial systolic murmur is recorded.

The heart sounds and murmurs of atrial septal defect are shown by phonocardiography to be characteristic. They can usually be recognized by auscultation and should prove to be of help in the clinical diagnosis.

We wish to thank the physicians of the National Heart Hospital for allowing us to investigate and present their cases. We are also grateful to Dr. Paul Wood and Dr. William Evans for much helpful criticism. We are much indebted to the technical staff of the Institute of Cardiology for their assistance in making the recordings.

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ATRIAL SEPTAL DEFECT

BY

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Atrial septal defect is one of the common types of congenital heart disease. Although recognized for centuries and receiving increasing attention since 1900, it was the detailed description by Bedford, Papp, and Parkinson in 1941, of the physical, electrocardiographic, radiological, and diagnostic features, the complications, and the clinical course, that brought the salient characteristics of this disorder to the attention of the medical profession. More recently, with the advent of new techniques of investigation, many publications have described the pathological physiology of the disease (Howarth *et al.*, 1947; Barber *et al.*, 1950; Lequime *et al.*, 1950; Soulié *et al.*, 1950; Puddu, 1952; Limón Lasón *et al.*, 1953; Heim de Balzac *et al.*, 1954). Finally, the introduction of surgical correction has given impetus to further inquiries into its many facets.

As Bedford, Papp, and Parkinson pointed out, there are a number of complications that occur and lead to varying degrees of incapacity—complications that may well have an important bearing on the risk of surgical intervention. It seems timely, therefore, to inquire further into the nature of this disorder and some of its complications—(1) hypoxæmia giving rise to cyanosis, (2) pulmonary vascular disease, (3) right ventricular failure, (4) left ventricular failure, and (5) mitral stenosis or Lutembacher's syndrome.

Material

Sixty patients have been studied by cardiac catheterization, as described elsewhere (Dexter *et al.*, 1947). Seven of these patients were studied twice. There were 42 females and 18 males, ranging in age from 3 to 57 years.

Calculations of blood flow in patients with atrial septal defect are fraught with error. The narrow arteriovenous oxygen difference between pulmonary vein and artery associated with large pulmonary blood flows seriously interferes with the accuracy of the calculation by the Fick method. One may, in fact, be confronted with the distressing circumstances of having an arteriovenous oxygen difference so narrow as to be undetected by Van Slyke oxygen analysis, thus resulting in the calculation of an infinite pulmonary blood flow. There is no adequate site for obtaining mixed venous blood for the calculation of left ventricular cardiac output. We have used the superior vena cava. Errors involved in the calculation of ventricular outputs and shunts have been described in some detail (Dexter *et al.*, 1947). These errors, however, do not detract from the usefulness of such measurements because they reflect large, medium, or normal right ventricular outputs; large, medium, or small left-to-right shunts; left ventricular outputs that at least are not raised and are in all probability subnormal; and right-to-left shunts that are small. The associated calculations of work and resistances necessarily suffer from the lack of precision of flow measurements, but it is believed that they are of similar value.

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Pathological Physiology of Atrial Septal Defect

Fig. 1 summarizes the salient findings in our patients, and Fig. 2 is a schema of the circulation in atrial septal defect. The atrial defect may vary in size from that of a small patent foramen ovale to complete absence of the septum. When the septal defect is small, the pressure in the left atrium is greater than in the right, and it is this pressure difference that has usually been considered to be responsible for the left-to-right shunt (Brannon *et al.*, 1945; Cournand *et al.*, 1947; Handelsman *et al.*, 1948; Little *et al.*, 1949; Wood, 1950; Martin and Essex, 1951; Calazel *et al.*, 1951; and

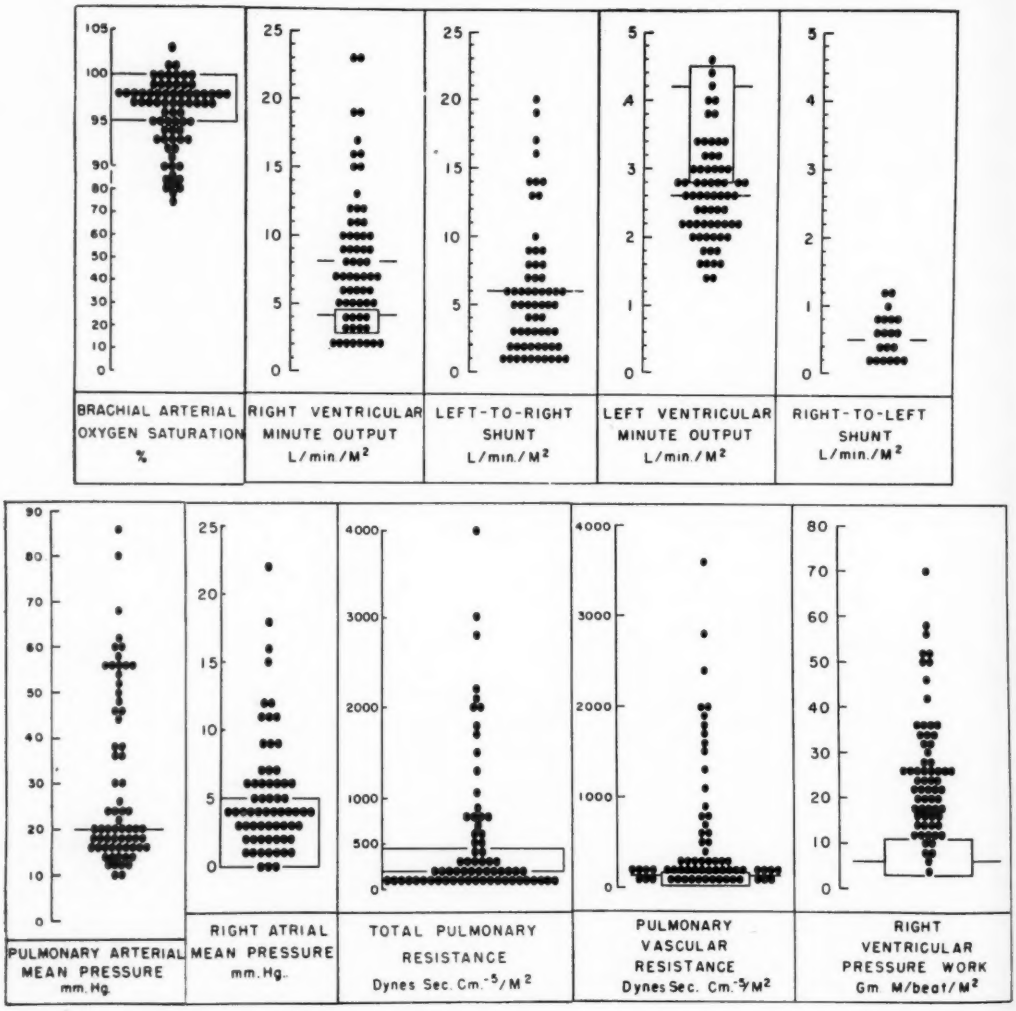
BRACHIAL ARTERIAL OXYGEN SATURATION %
RIGHT VENTRICULAR MINUTE OUTPUT L/min./M²
LEFT-TO-RIGHT SHUNT L/min./M²
LEFT VENTRICULAR MINUTE OUTPUT L/min./M²
RIGHT-TO-LEFT SHUNT L/min./M²
PULMONARY ARTERIAL MEAN PRESSURE mm.Hg.
RIGHT ATRIAL MEAN PRESSURE mm.Hg.
TOTAL PULMONARY RESISTANCE Dynes Sec. Cm.⁻⁵/M²
PULMONARY VASCULAR RESISTANCE Dynes Sec. Cm.⁻⁵/M²
RIGHT VENTRICULAR PRESSURE WORK Gm. M/beat/M²

FIG. 1.—Circulatory findings in atrial septal defect. Summary of the salient features in 67 studies of 60 patients. The open boxes in each diagram represent the normal variations obtained under the same conditions of rest in this laboratory.

Cosby *et al.*, 1952). When the septal defect is large, however, there is a free communication between both atria and their respective venous systems and, during diastole, their respective ventricles, both in experimental animals (Dow and Maloney, 1950) and in man. Using highly sensitive manometers capable of recording pressure differences of less than 0·5 mm. Hg accurately, no difference has been detected between left and right atrial pressures at the end of diastole in eight of our

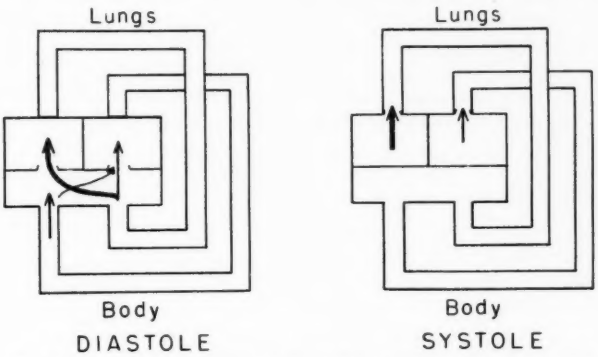

FIG. 2.—Schematic representation of the circulation in cases with a large atrial septal defect. *Left*. During diastole, pressures are almost identical in both ventricles, the common atrium, and both venous systems. The right ventricle, being more distensible than the left, fills to a much greater degree than the left at the same filling or diastolic pressure. As indicated by the heavy arrow, this results in a large left-to-right shunt. In some cases there is a bi-directional shunt and in others a right-to-left shunt alone (see text for discussion). The right-to-left shunt is always small. *Right*. During systole, each ventricle discharges the blood received during diastole into its respective circuit. The left-to-right shunt at the atrial level, taking place during systole, can get no farther than the right atrium, since the mitral and tricuspid valves are closed.

cases, in two it was less than 1·0 mm. Hg, in one it was 2 mm. Hg, and in two it was 3 mm. Hg. The average difference between left and right atrial end-diastolic pressure was 0·7 mm. Hg. In the instances where pressures were satisfactorily measured, no difference of pressure was found between left ventricular and left atrial end-diastolic pressure in 11 cases or between right ventricular and right atrial end-diastolic pressure in 31 cases.

In patients with the largest left-to-right shunts, mean and end-diastolic pressures in the two atria have uniformly been found to be identical, confirming the suggestion of Barger *et al.* (1948) and of Hull (1949) that the main cause of the left-to-right shunt in patients with atrial septal defect is the greater distensibility of the right ventricle than the left when confronted with equal filling pressures (Dow and Dexter, 1950).

When the atrial septum is intact, pressure in the left atrium is normally 5 mm. Hg or more higher than in the right. In the presence of a small atrial defect, this pressure gradient is maintained to a variable degree, depending on the size of the defect. With large defects of over two sq. cm., the pressure difference between the two atria is practically abolished.

It is concluded that when septal defects are large, pressures in both atria and both ventricles, and both venous systems become equal at the end of diastole; when the defects are so small that a free communication does not exist, a pressure difference exists between the two atria during diastole approaching the pressure difference that normally exists between the two sides of the heart in diastole.

The arrows in the schema represent the characteristic shunts in atrial septal defect. The main

shunt is from left to right and at times is enormous. This *left-to-right* shunt takes place mainly in *diastole*, when both venous systems, both atria, and both ventricles are in free communication. During systole, mitral and tricuspid valves close and both ventricles eject their contents into their respective arterial systems. The right ventricular output, which may be huge, passes through the low resistance area of the lung and on into the common atrium. A variable proportion of this large flow then passes around and around this circuit, never getting out to the tissues of the body and representing only wasted energy expenditure on the part of the right ventricle.

Some patients have a small right-to-left shunt, as indicated by the smaller arrow in Fig. 2. Its nature and cause will be discussed more fully later. The left ventricular output, as calculated, is less than normal or at least is not raised and is remarkably constant from patient to patient.

Pressures in the right ventricle and pulmonary artery may be normal or variably raised. Modest rises of pressure may be explained solely by increased flow when this exceeds 10 litres/minute/sq.m. (Dexter *et al.*, 1950), and in these cases the calculated pulmonary vascular resistance is normal or low. In other cases the raised pressure may be all out of proportion to the increased flow. This is due to the presence of pulmonary vascular disease, which is one of the most serious complications of atrial septal defect. It obstructs the flow of blood through the lung and is best expressed physiologically by calculation of the pulmonary vascular resistance

$$PVR = \frac{PAm - LAm}{F} \times 1332$$

where PVR = the pulmonary vascular resistance, in dynes seconds cm.$^{-5}$/sq.m.
PAm = pulmonary arterial mean pressure, in mm. Hg.
LAm = left atrial mean pressure, in mm. Hg (or pulmonary "capillary" mean or, in the presence of a large atrial septal defect, right atrial mean pressure).
F = pulmonary blood flow, in ml./second/sq.m. body surface.
1332 = a conversion factor.

Cyanosis (Arterial Oxygen Unsaturation)

Cyanose tardive was first described by Bard and Curtillet (1889) and is a well-recognized complication of atrial septal defect. Of our 60 patients, 11 were clinically cyanotic and an additional 11 had decreased arterial oxygen saturation in a range in which cyanosis could not be detected clinically (Fig. 3). Studies by other investigators have indicated a far higher frequency of arterial

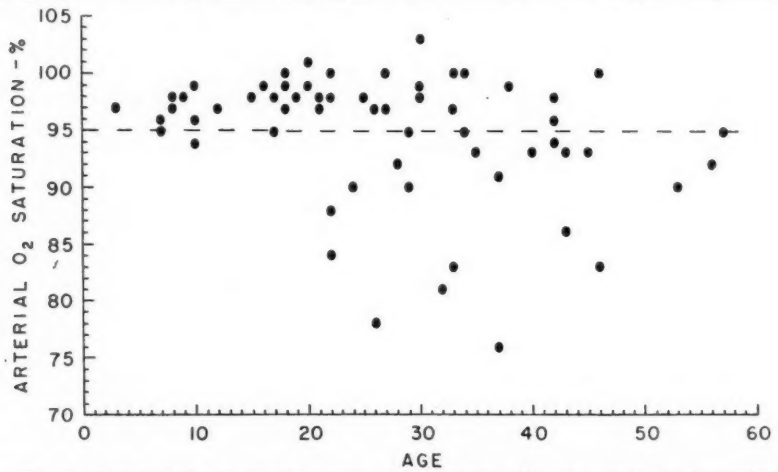

FIG. 3.—Relationship of arterial oxygen unsaturation with age. Note its increasing incidence with age and its rarity before the age of 20. Also observe that many patients in the older age group have a normal arterial oxygen saturation.

oxygen unsaturation, which we are inclined to attribute either to the high altitude at which the studies were undertaken or to the use of sedatives, which we have not used in this study for experience has indicated that they lead to inconstant and varying degrees of arterial oxygen unsaturation. Fig. 3 shows the relation of arterial oxygen saturation to age; two points are at once apparent. There are increasing numbers of patients with arterial oxygen unsaturation with the passing years —the well-known *cyanose tardive* of atrial septal defect. On the other hand, some patients do not develop it even into the fifth and sixth decades. We have not observed arterial unsaturation in the younger age group in uncomplicated atrial septal defect of the secundum type except in the one case in Fig. 3—a patient aged 10, with an arterial oxygen saturation of 94 per cent. Cyanosis from birth has been described (Selzer and Lewis, 1949), but is rare.

The possible causes of cyanosis are as follows.

(A) Defective diffusion of oxygen across the alveolar-capillary membrane.

(B) Incomplete oxygenation of blood, due to the large pulmonary blood flow.

(C) Mixing of both venous bloods in the common atrium.

(D) Reversal of shunt.

(A) The pulmonary venous oxygen saturation has been uniformly normal, or practically so, in patients with oxygen unsaturation of the arterial blood and with varying degrees of pulmonary vascular resistance (see Table I). This confirms similar findings of Limón Lasón and Alvarez

TABLE I

PULMONARY VENOUS OXYGEN SATURATION IN PATIENTS WITH BRACHIAL ARTERIAL OXYGEN UNSATURATION AT VARIOUS LEVELS OF PULMONARY VASCULAR RESISTANCE

Patient	Oxygen saturation (percentage)		Pulmonary vascular resistance (dynes sec. cm.$^{-5}$/m.^{2})
	Pulmonary vein	Brachial artery	
J.D.	99	92	79
S.W.	95	95	132
C.K.	100	93	461
M.M.	94	93	513
E.S.	100	94	1271
K.R.	98	86	1960
K.R.	99	83	1981
E.R.	99	83	2756

(1949) and of Soulié *et al.* (1954). From these data, it is concluded that there is no abnormality in the diffusion of oxygen across the alveolar-capillary membrane, even in the presence of severe pulmonary vascular disease.

(B) The greatest calculated pulmonary blood flows were not associated with arterial oxygen unsaturation, as shown in Fig. 4. This illustrates the tremendous reserve in the ability of the lung to oxygenate fully four to five times the amount of blood normally flowing through it.

(C) Minor degrees of arterial oxygen unsaturation were seen in a sizeable number of patients whose right ventricular outputs were of considerable magnitude (Fig. 4). This is interpreted as evidence that slight arterial unsaturation is attributable to mixing of both venous bloods in the common atrium, or perhaps to streaming of the blood from right to left sides of the common atrium (Selzer and Lewis, 1949; and Swan *et al.*, 1954).

(D) It is also to be noted in Fig. 4, however, that the smaller the right ventricular output, the more likely the appearance of arterial oxygen unsaturation. In fact the patients with arterial oxygen saturations less than 90 per cent were the ones who had the smallest right ventricular outputs. This suggests that the more severe degrees of unsaturation are attributable to reversal of the shunt due to a low right ventricular output. The absence of cyanosis in earlier years suggests that these patients formerly had had greater right ventricular outputs and that it was only when the right

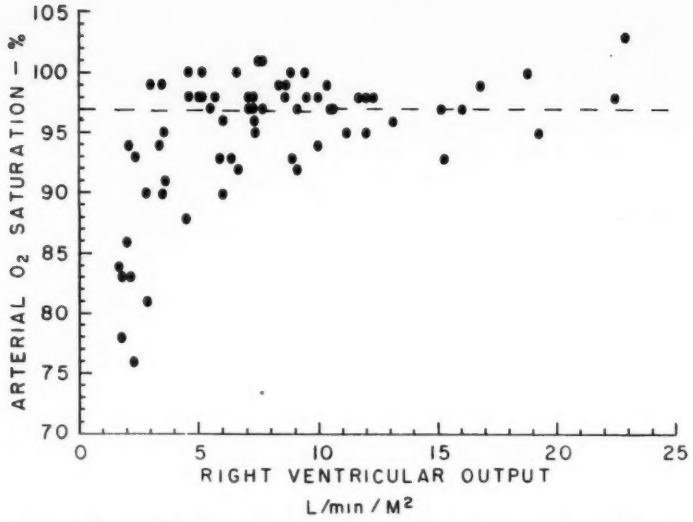

FIG. 4.—Relationship of arterial oxygen saturation to right ventricular output. The saturation is seen to be normal in most of those with huge pulmonary blood flows (or right ventricular outputs). Some patients have slight degrees of arterial oxygen unsaturation with high right ventricular outputs, but as the output of the right ventricle becomes less and less, approaching that of the left ventricle, the tendency to arterial oxygen unsaturation becomes more and more apparent. In this series, the most severe degrees of arterial oxygen unsaturation occurred in those with the smallest right ventricular outputs.

ventricular output approximated that of the left that a right-to-left shunt of sufficient magnitude to produce cyanosis occurred. In support of this, three patients who have been studied on two occasions 2 to 7 years apart have had a progressive fall of both arterial oxygen saturation and of right ventricular output (Table II). Such a reversal of shunt has usually been attributed to failure of the right ventricle leading to a higher pressure in the right than in the left atrium (Cournand *et al.*, 1947; Little *et al.*, 1949; Wood, 1950; Calazel *et al.*, 1951; and Cosby *et al.*, 1953). In 8 patients with arterial oxygen unsaturation, however, no measurable difference could be detected between the left and right atrial mean pressures in 4, and in 4 the mean pressures, as recorded, were 1 mm. Hg higher in the left atrium than in the right. In four cases the tracings were sufficiently satisfactory to measure the end-diastolic pressures. In three, they were identical and in one it was, as recorded, 1 mm. Hg higher in the left atrium than in the right.

TABLE II

FALL OF RIGHT VENTRICULAR OUTPUT WITH INCREASING ARTERIAL O_2 UNSATURATION

Patient	Year	Right ventricular output (litres/min./m.²)	Brachial arterial oxygen saturation (percentage)
E.R.	1948	7·1	97
	1955	1·8	83
F.S.	1946	5·0	98
	1953	3·6	91
A.B.	1950	6·0	90
	1952	2·9	81

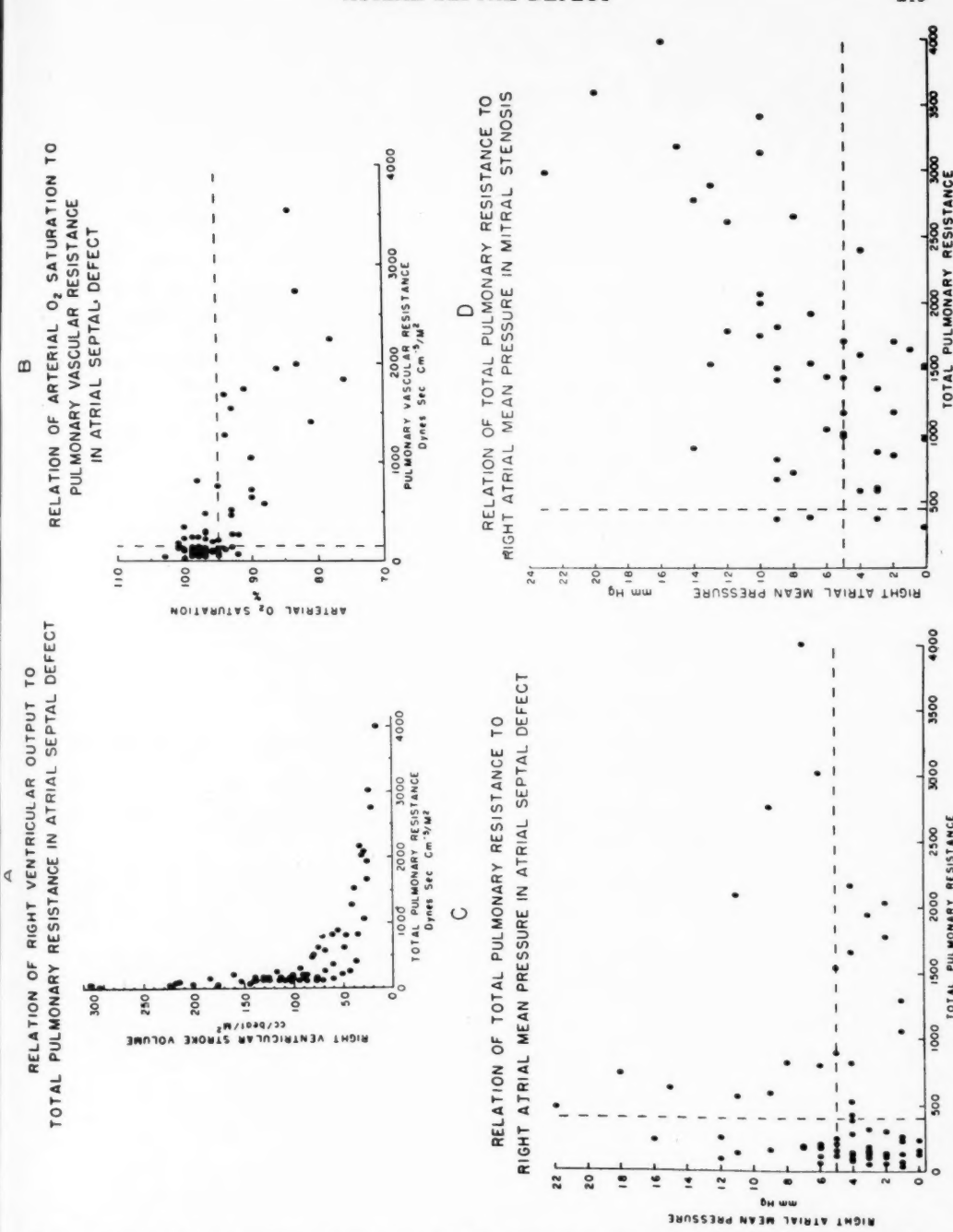
A
RELATION OF RIGHT VENTRICULAR OUTPUT TO TOTAL PULMONARY RESISTANCE IN ATRIAL SEPTAL DEFECT
RIGHT VENTRICULAR STROKE VOLUME
TOTAL PULMONARY RESISTANCE
B
RELATION OF ARTERIAL O2 SATURATION TO PULMONARY VASCULAR RESISTANCE IN ATRIAL SEPTAL DEFECT
ARTERIAL O2 SATURATION
PULMONARY VASCULAR RESISTANCE
C
RELATION OF TOTAL PULMONARY RESISTANCE TO RIGHT ATRIAL MEAN PRESSURE IN ATRIAL SEPTAL DEFECT
RIGHT ATRIAL MEAN PRESSURE
TOTAL PULMONARY RESISTANCE
D
RELATION OF TOTAL PULMONARY RESISTANCE TO RIGHT ATRIAL MEAN PRESSURE IN MITRAL STENOSIS
RIGHT ATRIAL MEAN PRESSURE
TOTAL PULMONARY RESISTANCE

FIG. 5.—(A) As total pulmonary resistance rises, the right ventricular output falls. (B) As pulmonary vascular resistance rises, arterial oxygen unsaturation becomes more pronounced. (C) The highest diastolic pressures occurred in those patients with a minimal, if any, increase of total pulmonary resistance. In patients with the highest resistances, the right atrial pressure was only slightly raised. In these patients with an atrial septal defect, there is thus no relationship between total pulmonary resistance and the right atrial mean (or right ventricular diastolic) pressure. (D) In patients with mitral stenosis and an intact atrial septum, the direct relationship between right atrial pressure and total pulmonary resistance is apparent.

In summary, minor degrees (and probably major degrees on occasion) of arterial oxygen unsaturation are due to mixing of systemic and pulmonary venous blood streams in the common atrium in these patients with atrial septal defect, while the more severe degrees manifested by clinical cyanosis are usually associated with a low right ventricular output with a reversal of shunt but *not* associated with a higher pressure in the right atrium than in the left. It seems probable that as the outputs of the two ventricles approximate one another, mixing of the two venous blood streams is enhanced in the common atrium.

Although there are several possible causes of a progressive diminution of right ventricular output in these patients, one of the most important is the presence of an increase of pulmonary vascular resistance. This is not a unique relationship confined to patients with atrial septal defect. Exactly the same relation holds in pulmonary vascular disease from any cause (Dexter, 1951) including mitral stenosis (Gorlin *et al.*, 1951). Fig. 5A shows that the higher the pulmonary resistance, the lower the right ventricular output. From the foregoing considerations, it then follows that the higher the pulmonary vascular resistance, the greater the tendency to arterial oxygen unsaturation (Fig. 5B). It has been demonstrated (Table I) that the unsaturation is not produced in the lung itself but only secondarily through the effect of an increased resistance in drastically reducing the right ventricular output; this facilitates mixing of systemic and pulmonary venous bloods in the common atrium and, in turn, leads to a right-to-left shunt. This leads, therefore, to a consideration of pulmonary vascular disease as it occurs in patients with atrial septal defect.

Pulmonary Vascular Disease

In 36 of the 67 studies, the pulmonary vascular resistance was considered to be normal, i.e. less than 160 dynes seconds $cm.^{-5}/m.^2$ (see Fig. 2). In 31, the value was above this figure. In 18, it exceeded 500, in 12 it exceeded 1000, roughly 10 times or more the normal; the highest value was 3530. These resistance figures give a rough measure of the difficulty blood encounters in passing through the pulmonary vasculature. The clinical importance of pulmonary vascular disease is that it is consistently associated with limitations heretofore absent and produces a progressively down-hill course culminating in death.

Vessels of the normal lung offer very little resistance to blood flow. The right ventricle can pump up to 10 litres/minute/sq.metre through the lung at relatively normal pressures (Dexter *et al.*, 1950). The main circulatory effects of any type of obstruction in the central circulation such as the raised pulmonary vascular resistance in atrial septal defect are twofold. There is a reduction of blood flow and the pressure rises proximal to the obstruction. In the case of atrial septal defect, the pulmonary flow declines (Fig. 5A) and the pulmonary artery and right ventricular pressures rise (see Fig. 1).

A real increase of pulmonary vascular resistance has rarely been observed by us before the age of 20 (Fig. 6). Two patients, age 3 and 8, had a resistance of about twice normal: another had a similarly borderline elevation at the age of 12, but on restudying him at 17, an entirely normal value was found. The only patients of young age that we have seen with extremely high resistances have been those with an ostium primum type of defect or those with small atrial defects with what was interpreted as being primary pulmonary vascular disease. After the age of 20, an increased vascular resistance may or may not be present (Fig. 6); some of our patients in the fifth and sixth decades had normal resistances and some were raised. The lines with arrows in Fig. 6 represent our experience on restudying a small number of patients and demonstrate the increase of resistance that occurred over the span of a few years. This evidence seems to indicate that the increase of pulmonary vascular resistance in patients with atrial septal defect is an acquired abnormality affecting some but not all of the cases.

The nature of the increased pulmonary vascular resistance has been and is being the subject of intensive investigation on the part of many. Intimal proliferation of the pulmonary arterioles and small arteries occurs (Edwards, 1950; Evans, 1951; and personal observations) but, as in the case

of systemic hypertension, it is not clear whether these lesions are the cause or the result of the pulmonary hypertension. Their distribution is patchy and not uniform. Vasoconstriction of the pulmonary vessels remains suspect but unproven. Although there is an increasing body of evidence suggesting that under certain circumstances the pulmonary vessels have powerful vasomotor activity, its nature, pharmacological response, and precise manner of behaviour are among the most important problems confronting the circulatory field at this moment. Wood (1952) has

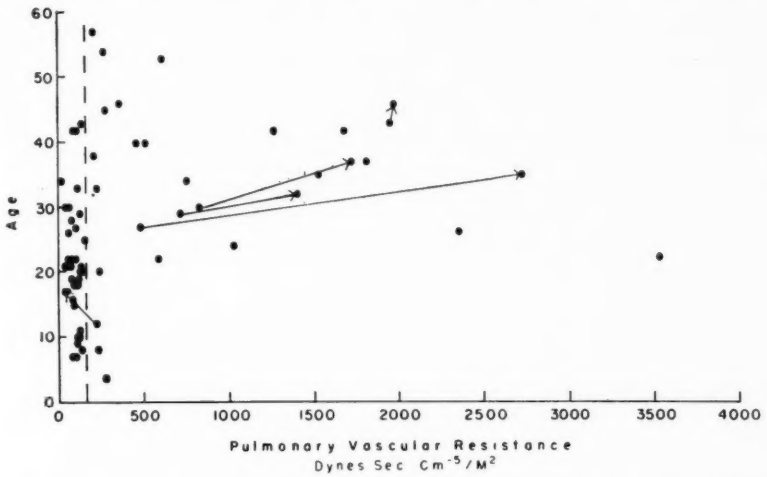

FIG. 6.—Relation of pulmonary vascular resistance to age. The vertical interrupted line represents the arbitrary upper limit of normal pulmonary vascular resistance. Note that in this series no real increase of resistance was found before the age of 20, and that there was a progressive increase in those studied on subsequent occasions, as indicated by the arrows. Observe also that many patients even in the fourth and fifth decades had normal values for pulmonary vascular resistance.

observed that only 10 to 15 per cent of patients with lesions capable of provoking pulmonary vascular disease (atrial septal defect, ventricular septal defect, patent ductus arteriosus, mitral stenosis, etc.) actually develop severe grades of this vascular disorder. A corollary of this important observation is that in a similar proportion of patients with these same provocative stimuli, pulmonary vascular disease never develops.

Edwards (1950) has cited evidence to show that in Eisenmenger's syndrome, the high pulmonary vascular resistance is present at birth and represents a persistence of the fœtal type of vasculature which, during fœtal life, is a vasculature of high resistance. I am not aware that this has been demonstrated to occur in patients with atrial septal defect, but it has been suggested by Wood (1952), Evans, (1951), and others that the pulmonary vascular disease of atrial septal defect may have been on the basis of a congenital predisposition. Our own limited experience does not negate this thesis, but, as shown in Fig. 6, we have not found supporting evidence.

Thrombosis of the pulmonary vasculature has been demonstrated as a late event in many cases of atrial septal defect (Bedford *et al.*, 1941; Evans, 1951; Massee, 1947; and personal observations) as well as of Eisenmenger's syndrome (Edwards, 1950) and occasionally patent ductus arteriosus associated with high pulmonary pressures (Chapman and Robbins, 1944; Douglas *et al.*, 1947; Edwards *et al.*, 1949). This, of course, produces a mechanical block to flow in all areas occupied by the thrombus. Sometimes the process is so extensive as to produce at necropsy a cast of the whole pulmonary arterial tree (Massee, 1947; and personal observations). How much benefit can be expected from prolonged anticoagulant therapy is problematical. It seems likely that extension

of thrombosis can be prevented, but whether resolution or effective recanalization of the thrombus can be promoted seems doubtful. The unhappy circumstance is that the cross-sectional area of the pulmonary arterial tree must be reduced by two-thirds before a rise of pulmonary arterial pressure or a reduction of flow appear (Gibbon *et al.*, 1932). In other words, no change in calculated resistance appears until the process is advanced. One cannot but wonder how many of our cases whose pulmonary vascular resistance was only slightly raised already had extensive thrombosis of the pulmonary vasculature.

The importance of this complication cannot be over-emphasized. From a surgical viewpoint, our limited experience and that of others (Swan, 1953; Bailey *et al.*, 1954; and Kirklin *et al.*, 1955) indicates that the risk of surgery rises *pari passu* with the severity of the pulmonary vascular disease, being prohibitive in the far-advanced cases. The reversibility of the pulmonary vascular disease associated with mitral stenosis by mitral valvotomy cannot be used as an argument that the pulmonary vascular disease of atrial septal defect will be similarly reversible following closure of the septal defect. The thrombotic nature of the pulmonary vascular disease of atrial septal defect is characteristically not seen in patients with mitral stenosis.

Thus, an important unsolved problem associated with atrial septal defect is the complication of the pulmonary vascular disease, its nature, pathogenesis, prevention, control and its reversibility.

Ventricular Function

Ordinarily, the heart does not fail as a whole. The two sides fail in a separate fashion. The clinical manifestations of left ventricular failure are those of pulmonary congestion, and of right ventricular failure, systemic venous congestion. When a ventricle fails, there are two fundamental ways in which it can react—the first is a reduction of work load or output, the second is dilatation or stretching of the muscle fibre to increase the force of contraction (Patterson and Starling, 1914; and Lewis *et al.*, 1953). If it dilates, it is an increase of diastolic pressure, ultimately produced by the other ventricle, that produces the dilatation. Thus, as ventricles fail, their work load or output may become reduced or their diastolic pressure may rise, or usually both occur.

As has been pointed out, in atrial septal defect the two ventricles can be considered to be in free communication during diastole. The problem arises as to which ventricle controls the diastolic pressure. Does right ventricular failure result in a rise of the diastolic pressure of the right ventricle and atrium as well as in the left ventricle and atrium, or is it with failure of the left ventricle that these pressures rise? There are three points of evidence indicating that when the right ventricle fails, its diastolic pressure remains unchanged and its output becomes reduced; but that when the left ventricle fails, its output, already low, is relatively unaffected (although there is a tendency for it to become slightly lower), the main effect being reflected in a rise of diastolic pressure. In so doing, the pressure in diastole rises in both atria, both ventricles, and both venous systems, with resultant congestion of pulmonary venous and systemic venous compartments. The evidence is as follows.

(*a*) The diastolic pressure in the two ventricles in relation to their output is shown in Fig. 7. As indicated by the crosses and the straight line, the left ventricular stroke output remains fairly constant over a wide range of diastolic pressure. At the higher diastolic pressure levels, the left ventricles are failing in the physiological sense that they are performing a subnormal amount of work at a filling pressure higher than is their wont and higher (by history) than they previously had had. Whether this is to be called ventricular failure or malfunction or by some other term is of little importance. We have chosen to call it failure until evidence is forthcoming that it is on some other basis. The important point is that in left ventricular failure, the output remains relatively stable only at the expense of a rise in diastolic filling pressure. On the other hand, as indicated by the dots in Fig. 7, there is no relationship whatever between the diastolic pressure in the right ventricle and its output (or, not shown here, pressure work). The right ventricle may eject large volumes of blood at low or high diastolic pressures, or small volumes at low or high diastolic pressures. In other words, these data show that the peripheral demands for blood continue to be met by a failing left ventricle by an elevation of its diastolic pressure, whereas the total lack of

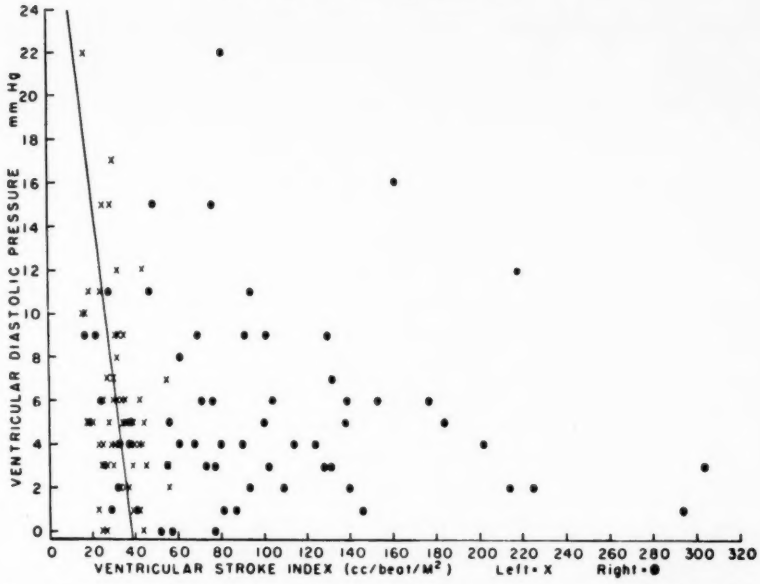

FIG. 7.—Relation of ventricular diastolic pressure to stroke volume of right and left ventricles. Left ventricular stroke volume (X), already small, tends to become slightly smaller as left ventricular diastolic pressure rises. This shows that peripheral tissue needs for blood are fulfilled, but only through the mechanism of myocardial stretching (elevated diastolic pressure) which produces a more effective left ventricular systolic discharge (Patterson and Starling, 1914). There is no relationship whatsoever between right ventricular stroke volume (·) and its diastolic pressure.

relationship between right ventricular output and its diastolic pressure indicates that the right ventricle, having no control over its own filling pressure, behaves quite differently. These peculiarities will be discussed in more detail later.

(*b*) Pulmonary vascular disease is recognized to be a common cause of right ventricular failure (Dexter, 1951; and Lewis *et al.*, 1952). It can be assumed to cause such failure in atrial septal defect. Fig. 5 shows the relation between an increase of pulmonary resistance on the one hand and right ventricular output and diastolic pressure on the other. There is a close inverse relation between pulmonary resistance and right ventricular output in these cases (Fig. 5A), but none whatsoever between the resistance and the right ventricular diastolic pressure (Fig. 5C). In other words, a complication known to cause failure of the right ventricle reduces the output of the right ventricle but appears to have no effect on its diastolic pressure. This is in striking contrast to mitral stenosis, with an *intact* septum, wherein the same relationship between total pulmonary resistance and reduced right ventricular stroke output holds (Gorlin *et al.*, 1951), but the right ventricular diastolic pressure rises as the pulmonary resistance rises (Fig. 5D).

(*c*) The effect of acute digitalization on the hæmodynamics of eight patients with atrial septal defect has been studied. Administered to patients with normal hearts, digitalis causes a slight reduction of cardiac output and no significant change of ventricular pressure (Stewart *et al.*, 1938). In the presence of heart failure, ventricular diastolic pressure falls and cardiac output increases (Stewart and Watson, 1938). Thus, digitalis is a useful agent for evaluating ventricular function, and we have applied it to the study of ventricular function in atrial septal defect. The left-hand columns of Fig. 8 show that the first four patients had no significant change of right ventricular output after acute digitalization. Three of these cases had no significant change of diastolic

pressure, as indicated by the numbers above the columns and as nearly as could be determined were cases of uncomplicated atrial septal defect. The fourth (E.R.) had severe pulmonary vascular disease with a pulmonary vascular resistance of 2756 dynes seconds cm.$^{-5}$/m.^{2} The next four patients had striking increases of right ventricular output without significant change of diastolic pressure in three and with a fall of diastolic pressure from 8 to 4 mm. Hg in the first patient (D.K.). These findings indicate that if the right ventricle is competent, or if it is confronted with an extremely high pulmonary vascular resistance, acute digitalization has no effect on right ventricular output

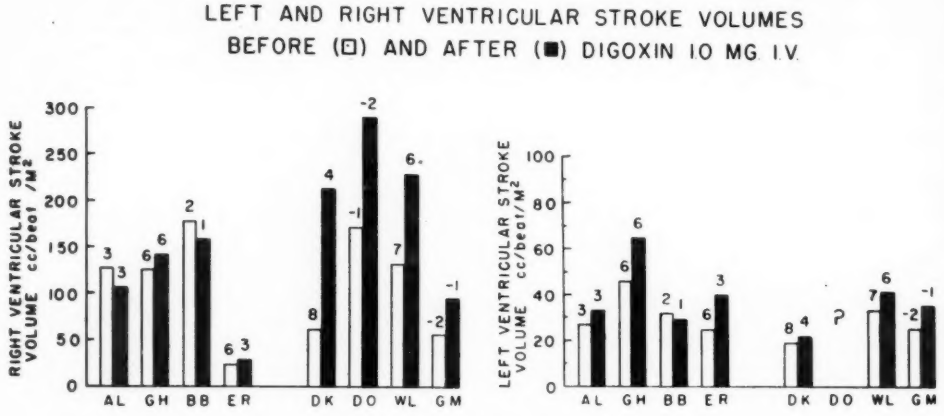
LEFT AND RIGHT VENTRICULAR STROKE VOLUMES
BEFORE (□) AND AFTER (■) DIGOXIN 10 MG. I.V.
RIGHT VENTRICULAR STROKE VOLUME cc/beat /M²
LEFT VENTRICULAR STROKE VOLUME cc/beat/M²
AL GH BB ER DK DO WL GM

FIG. 8.—The effect of digitalis on right and left ventricular stroke volumes before (open columns) and 45 minutes after (black columns) the administration of 1·0 mg. digoxin intravenously. Numbers above the columns represent diastolic pressures. (See text for discussion.)

and diastolic pressures. If, on the other hand, the right ventricle has failed, there is an impressive increase in its output with no convincing change (in three out of four studies) of its diastolic pressure.

The effect of digitalis on left ventricular behaviour has not been well demonstrated so far because all cases with high diastolic pressures have had prior treatment with digitalis and thus could not be utilized for this special type of study. What results we have are shown in the seven columns on the right side of Fig. 8. There was a general tendency for left ventricular output to increase in six of the seven studies, but it should be noted that these increases were well within the error of the method in all but the second and perhaps the fourth case. In one patient (D.K.) there was a significant fall of diastolic pressure from 8 to 4 mm. Hg. In one other (E.R.) there was a decrease from 6 to 3 mm. Hg.

These findings indicate that if the left ventricle is competent, digitalis has no significant effect upon either its output or its diastolic pressure. If incompetent, as in one case in borderline failure, indicated by a diastolic pressure of 8 mm. Hg, digitalis produced no significant increase of output but did result in a fall of diastolic pressure from 8 to 4 mm. Hg.

These observations raise an interesting point for speculation with respect to the advisability of digitalization of these patients. It would appear that digitalis increases the output of failing right ventricles, but in so doing it increases the left-to-right shunt and the pulmonary blood flow. Whether or not this is a beneficial effect is not elucidated by our studies.

Fig. 9 is a schema to illustrate our concept of ventricular behaviour in the presence of large atrial septal defects, based on the data cited above. Uncomplicated atrial septal defects with competent left and right ventricles might be considered to have atrial and ventricular diastolic pressures of 2 mm. Hg, a right ventricular output of 18 litres/minute, and a left ventricular output of 5 litres/minute. With failure of the left ventricle, the diastolic pressure rises, and this rise is shared by

both atria and both venous systems as well as the right ventricle during diastole. The left ventricular output is constant or at most declines only slightly, the right ventricular output theoretically increases slightly (from 18 to 20 litres/minute in this illustration) due to the increased stretch of muscle fibre from elevation of its diastolic pressure. With failure of the right ventricle, on the other hand, there is no change of its diastolic pressure or of that in the atria. Instead, its ability to empty itself during systole is imperfect and as it fails progressively, the residual volume increases and the stroke volume decreases.

The clinical implications of these observations are that manifestations of left ventricular failure

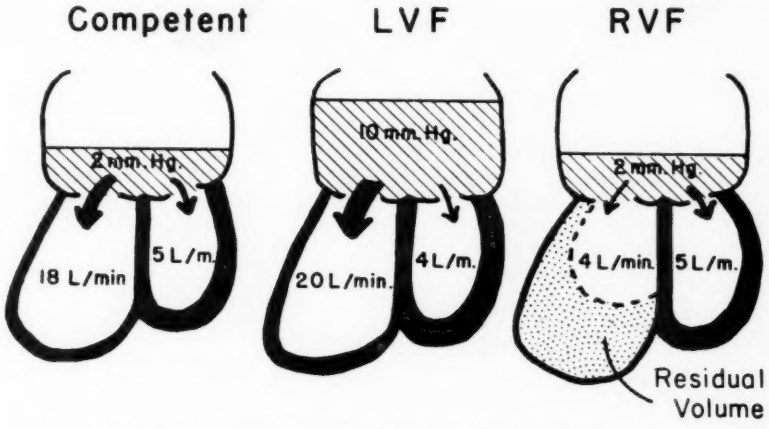

FIG. 9.—Schematic representation of ventricular function in the presence of an atrial septal defect. (See text for discussion.)

consist of congestion of both the pulmonary and systemic venous circuits. Right ventricular failure consists of a reduction of right ventricular output with an eventual reversal of shunt and cyanosis but no increase of its diastolic pressure and therefore no systemic venous congestion. Even tricuspid regurgitation, which must be a common complication of an atrial septal defect, has no effect on the right ventricular diastolic pressure or on the systemic venous pressure; its effect is merely to reduce the right ventricular output into the pulmonary artery.

RIGHT VENTRICULAR FAILURE

There are three obvious causes of right ventricular failure in these patients. One is the amount of work (pressure × flow) that the right ventricle performs. This calculation does not take into account the kinetic energy involved in imparting velocity to the huge flow of blood by the right ventricle. Ordinarily this is of little importance, but in these cases it must represent a tremendous expenditure of energy on the part of the right ventricle. In only six of our cases was the right ventricular pressure work load normal (see Fig. 1). In the remainder it was variably raised, the highest being over seven times the normal. In the uncomplicated cases, the increased work is largely flow work, which in general is well tolerated. Pressure work, however, is badly tolerated (Evans and Matsuoka, 1915). Thus, a second cause of right ventricular failure is the appearance of pulmonary vascular disease. In cases in whom this complication occurs, the work load on the right ventricle changes gradually from flow work to pressure work. It is in great part this effect which makes pulmonary vascular disease such a vicious complication. A third cause of right ventricular failure is tricuspid incompetence due to functional dilatation of the tricuspid ring and orifice. How often this occurs is difficult to state, as it may or may not be related to the presence or absence of pulmonary hypertension. Lack of descent of the *c* wave in the right atrial pressure tracing is

usually considered to be the earliest sign of its presence (Bloomfield *et al.*, 1946). A high *v* wave is occasionally found. None of our patients had high *v* waves and only four had a lack of descent of the base. Only three had systolic pulsations of the liver. Thus, only a few patients had clinical or manometric evidence of tricuspid incompetence. It is assumed, however, that with a ventricle as dilated as that found characteristically in patients with atrial septal defect, tricuspid incompetence is a far commoner lesion than our findings would suggest. The inability to detect positive evidence of its presence may be attributable to the damping of regurgitant pressure waves by the combined volume of both atria and both venous systems into which the regurgitant blood is ejected. It is also apparent that the problem of differentiating tricuspid incompetence from mitral incompetence is difficult because the regurgitant streams through the orifice of both valves enter the same common atrium and both venous systems. In three of the six patients in whom clinical or hæmodynamic evidence of incompetence was considered to be present, operative or necropsy findings indicated the presence of *mitral* regurgitation. Thus, although tricuspid regurgitation is presumably present fairly commonly in patients with atrial septal defect, it has been identified only occasionally and even then has been difficult to differentiate from mitral incompetence.

How many of our patients had malfunctioning right ventricles is impossible to say. Short of the appearance of cyanosis, there is at present no means of recognizing a poorly functioning right ventricle except to study the effect of digitalis on the right ventricular output and shunt, and this is a cumbersome and laborious procedure.

Left Ventricular Failure

The question may well be asked why the left ventricle should fail in patients with atrial septal defect in which the left ventricle is by-passed by the shunt and does less work than it is normally expected to do. Fourteen of our cases had atrial pressures above 6 mm. Hg and the causes of this elevation were as follows

Atrial pressure greater than 6 mm. Hg (14 patients).
- Demonstrable or possible rheumatic heart disease (9 patients).
  - Loud apical pansystolic murmurs and rheumatic deformity of mitral valve without stenosis at necropsy (4 patients).
  - Loud pansystolic apical murmur; X-ray calcification of mitral valve; no necropsy (1 patient).
  - Loud apical pansystolic murmurs, but no history of acute rheumatic fever and no necropsy (2 patients).
  - History of acute rheumatic fever, one with and one without a loud apical pansystolic murmur; no necropsy (2 patients).
- Endocardial fibroelastosis of left ventricle with normal mitral valve at necropsy (1 patient).
- Hypertension (140/110) (1 patient).
- Uncertain cause; no clinical clues; no necropsy (3 patients).

All five necropsied patients had demonstrable lesions imposing a strain on the left ventricle, another had calcification of the mitral valve radiologically, and another had systemic hypertension. Four other cases were suspected clinically of having similar lesions, and in only three was there no clue. In all cases, the suspected or demonstrated lesions affecting the left ventricle were relatively minor. It is doubtful if they would have caused significant disability in a normal heart, but they appear to be serious in these patients whose left ventricles are characteristically small and hypoplastic. In several of these cases, roentgen examination during life revealed left ventricles that appeared to be dilated. Post mortem, however, they had a small cavity and were hypoplastic. As far as I have been able to ascertain, their pressure-volume characteristics have never been studied and it is therefore difficult to decide whether or not during life they were actually larger because of their raised filling pressures and incomplete emptying, or were only apparently enlarged because of distortion of the cardiac silhouette by the tremendously enlarged right hearts.

Another explanation for the malfunction of the left ventricle has been the reverse of Bernheim's syndrome, i.e. the encroachment on the left ventricular cavity by the interventricular septum, causing an interference with filling. In two of our patients, Dr. Dwight E. Harken palpated the mitral valve and the cavity of the left ventricle during exploratory cardiotomy and described the

obliteration of the left ventricular cavity by the septum. Just how much this would actually affect left ventricular function has not been investigated.

Another suggestion (Donovan, 1953; Wood, 1955; and Dornhorst, 1955) has been the limitation of left ventricular filling by the tension created by an over-stretched pericardium, resulting from the tremendous dilatation of the right heart. Against this explanation is that given time, as in these cases, the pericardium is capable of tremendous stretch, in contrast to its limited stretching capacity if the time course is short, as in cases of pericardial effusion or hæmopericardium. In five cases with raised atrial pressures the pericardium was not tense at the time of surgery. In fact, it was lax. The heart did not herniate through the incised pericardium as it frequently does in patients with constrictive pericarditis. Furthermore, there has been a poor correlation between heart size and atrial and ventricular diastolic pressures. Some of the biggest hearts in this series have had relatively normal diastolic pressures and some of those with a high atrial pressure have had a heart that was only slightly enlarged.

Our experience, therefore, indicates that relatively minor lesions imposing a burden on the left ventricle seem to be capable of causing the hypoplastic left ventricles of atrial septal defect to fail in the sense that there is a decreased work performance in the face of an abnormally high diastolic filling pressure. In each of five patients coming to necropsy with this complication, left ventricular lesions were demonstrable. A reverse of Bernheim's syndrome cannot be excluded, but seems unlikely as a basic factor; if it were, this complication would be expected to be more frequent and would be expected to bear a closer relation to heart size. Our observations give no support to a pericardial factor.

Lutembacher's Syndrome

Mitral stenosis associated with atrial septal defect produces the same hæmodynamic change as does left ventricular failure except for the fact that the left ventricular diastolic pressure remains normal. The pressure in the left and right atria, right ventricle, and both venous systems rise. Tight mitral stenosis in association with atrial septal defect is rare (Nadas and Alimurung, 1952). We have seen two patients with large atrial septal defects and severe mitral stenosis, only one of whom was studied in detail (Rapaport *et al.*, to be published). The differentiation of these cases from those with left ventricular failure has been difficult. In both there may be symptoms and signs of pulmonary and peripheral congestion, a loud apical first sound, an accentuated and split pulmonic second sound, an apical pansytolic murmur, and a classical mitral diastolic rumble with presystolic accentuation if the rhythm is regular, normal sinus rhythm or auricular fibrillation. An opening snap of the mitral valve was even heard in two patients who turned out not to have mitral stenosis (this latter observation was not checked by phonocardiography). Radiography, fluoroscopy, and electrocardiograms have yielded no differential features. The two conditions can be accurately differentiated only by cardiac catheterization. If the catheter can be passed through the atrial defect into the left atrium and thence through the mitral valve into the left ventricle, pressure records will reveal raised but equal diastolic pressures in the left ventricle and atrium in those cases with left ventricular failure, whereas in the presence of mitral stenosis, the left atrial diastolic pressure will be higher than the corresponding left ventricular pressure.

The importance of differentiating mitral stenosis from left ventricular failure in these cases is obvious. Relief of a severe mitral stenosis in two cases in our experience has resulted in dramatic clinical improvement. Complete closure of the atrial defect in seven patients who even after prolonged medical management in the hospital had markedly raised atrial pressure on the basis of left ventricular failure, has resulted in death in five. This is admittedly a small experience, but until now, at least, a discouraging one.

Summary

The salient circulatory changes in 60 patients with atrial septal defect have been presented. The hæmodynamic observations have elucidated certain features of the pathological physiology of

this condition. (1) A defect of sufficient size (>2·0 sq.cm. cross-sectional area) results in diminution or abolition of the normal atrial pressure difference between the two atria, producing a physiologically common atrium. (2) The left-to-right shunt is attributed to the different distensibility characteristics of the two ventricles such that at a common filling pressure the right ventricle achieves a far greater stroke volume than the left. (3) The magnitude of the left-to-right shunt, therefore, depends on the right ventricular output in relation to the left.

Information gained from this study has also clarified some of the physiological mechanisms underlying five complications that may or may not occur during the course of this disease: (1) *cyanose tardive*, (2) pulmonary vascular disease, (3) right ventricular failure, (4) left ventricular failure, and (5) mitral stenosis.

Cyanosis or arterial oxygen unsaturation is clearly due to a right-to-left shunt rather than to pulmonary factors. Minor degrees of unsaturation may be due either to random mixing of systemic and pulmonary venous blood in the common atrium or to a streaming effect. Severe degrees of unsaturation, on the other hand, are due to a decline in right ventricular output to a level approaching that of the left, thus facilitating interatrial mixing.

Pulmonary vascular disease is a vicious complication of atrial septal defect. In our experience its occurrence before adult life is exceptional. Pathologically it is characterized by obliterative intimal lesions and frequently by thrombosis of pulmonary arterial radicals, but its pathogenesis remains obscure. A rough estimate of its degree can be gleaned from the calculated pulmonary vascular resistance which in some cases may be enormous.

Right ventricular failure is most frequently a result of the increased pressure burden imposed by the development of pulmonary vascular disease, but also may be due to increased work or to tricuspid incompetence which clinically or physiologically may be impossible to differentiate from mitral incompetence. Right ventricular failure is characterized not by a raised diastolic pressure, but by a reduction in output leading eventually to a right-to-left shunt. The value of acute digitalization in assessing right ventricular function has been discussed.

Failure of the left ventricle in atrial septal defect has not as far as I know been described previously. We have observed this complication in 14 cases in this series. This is not surprising considering that the left ventricle is usually hypoplastic as a result of the by-pass just proximal to it. In our cases, left ventricular failure could usually be attributed to the existence of rather minor lesions that would ordinarily have little if any deleterious effect on left ventricular function. Physiologically, left ventricular failure is appreciated by a rise of diastolic pressure in the left ventricle as well as in both atria, both venous circuits, and right ventricle, and with only slight if any reduction in output.

Hæmodynamically significant mitral stenosis is a rare complication of atrial septal defect (Lutembacher's syndrome). Evidence indicates that it is extremely difficult, if not indeed impossible, to distinguish it from left ventricular failure unless the diastolic pressure gradient across the mitral valve is measured.

Over the past ten years, the part played by many colleagues too numerous to mention in the collection and interpretation of the material presented is acknowledged with gratitude and with a deep sense of indebtedness. Dr. Lawson McDonald contributed much to the recognition and understanding of the pathological physiology of mitral stenosis and left ventricular failure as it occurs in these patients. I am particularly under obligation to Dr. James W. Dow who, in 1949, studied the case material then available and reached many of the conclusions and interpretations presented here. Without his early unpublished contributions, this study would not have been possible.

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THE ELECTROCARDIOGRAM IN PNEUMOPERITONEUM, PNEUMOTHORAX, AND PHRENIC CRUSH

BY

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This study was undertaken in order to determine the electrocardiographic changes that take place in mechanical procedures that cause displacement of the heart such as pneumoperitoneum, artificial pneumothorax, and phrenic crush, and to decide if these procedures produced any evidence of cor pulmonale. A number of patients suffering from pulmonary tuberculosis who required artificial pneumoperitoneum or artificial pneumothorax or phrenic crush were studied. In each case cardiograms were taken in the supine position with one pillow under the head. Then the therapeutic procedure indicated was carried out, and when it was considered that the optimum effect had been secured further cardiograms were taken. In 10 instances, however, the control cardiograms were taken after the therapeutic procedure was discontinued and had apparently ceased to have any effect. Fifty-six patients were under the care of the author and full clinical data of these cases are available. In a further series of ten patients who were under the care of Dr. R. J. Grove-White and others at Tan Tock Seng Hospital, Singapore, clinical data were not obtained. Where several therapeutic measures were employed they were considered as separate cases.

The heights or depths of P, Q, R, S–T, and T were measured from the reference level of the T–P segment, i.e. just before the commencement of the P wave, and of the S–T segment at a point 0·04 sec. after the end of the QRS complex. All measurements of voltage were carried out with a Beck's illuminating hand microscope with a scale reading 1/10 mm. The shape of the S–T segments and T waves was studied with a hand lens. The P–R, Q–T, and R–R intervals were read in 1/100 sec. with a hand lens in standard limb lead II, and the Q–T ratio calculated from a nomogram (Goldberger, 1949). The cases were divided into the following groups:

		Cases
i	Pneumoperitoneum	38
ii	Pneumoperitoneum and right phrenic crush	16
iii	Right phrenic crush	15
iv	Right-sided artificial pneumothorax	10
v	Left-sided artificial pneumothorax	10
vi	Pneumoperitoneum and left phrenic crush ..	6
vii	Left phrenic crush	5
	Total	100

In assembling the data for assessment of their significance the following criteria were used: only differences of 1 mm. or more were considered significant in the case of P, Q, R, S, T, and S–T. In the case of the P–R interval a difference of 0·04 sec. or more and in the case of the Q–T ratio a difference of 0·02 or more were considered significant.

Results

There were no significant changes in the P wave, P–R interval, or the Q–T ratio. The S–T segment showed no significant elevation or depression and in no case did the S–T and T simulate the appearance seen in coronary disease. There was no evidence of cor pulmonale electrocardiographically or clinically. The main changes were in the QRS complex and are summarized as follows.

(i) Pneumoperitoneum produced an increase in the height of R in I, aVL, V2, V3, and V4 and a decrease in the height of R in II and aVF (Fig. 1–4).

(ii) Pneumoperitoneum and right phrenic crush produced an increase in the height of R in I, V2, and V4 and a decrease in the height of R in II, aVF, and III (Fig. 5 and 6).

(iii) Right phrenic crush produced a decrease in the height of R in V3 and V4 and an increase in the depth of S in V2.

(iv) Right-sided artificial pneumothorax produced an increase in the height of R in V4 and V5.

(v) Left-sided artificial pneumothorax produced a decrease in the height of R in I, V4, and V6 (Fig. 7–10).

(vi) Pneumoperitoneum and left phrenic crush produced an increase in the height of R in I, aVL, V2, V3, and V4 and a decrease in the depth of S in V1.

(vii) Left phrenic crush produced an increase in the height of R in I, and a decrease in the height of R in V4 and V6.

FIG. 1.—X-ray picture, showing tuberculosis of the right lung with a large cavity.

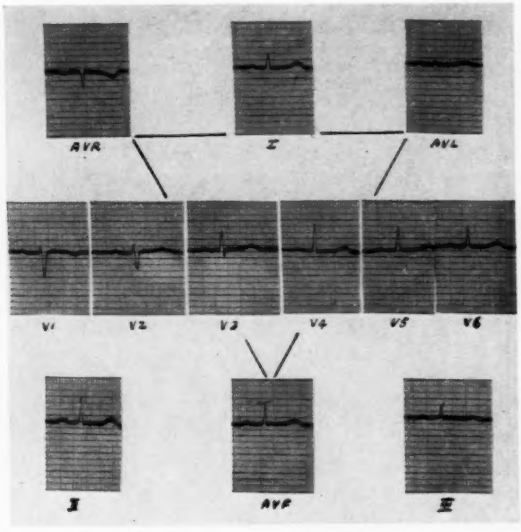

FIG. 2.—Electrocardiogram taken before treatment. aVL shows low R. V2 shows S>R. No Q in lead III.

Discussion

The mechanical principles governing the movement of the heart in the three planes should be considered. The heart is more or less tetrahedral in shape with the angles and margins rounded off, and its mobility is much greater at the apex than at the base, being restricted at the base by the attachment of the vascular pedicle. It is enclosed in a semi-rigid compartment—the thorax, and on either side are the spongy lungs which offer considerable resistance to shifting of the heart

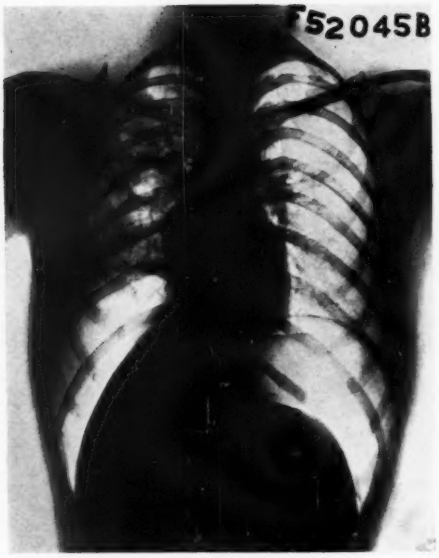

FIG. 3.—X-ray picture of same case as Fig. 1 after pneumoperitoneum.

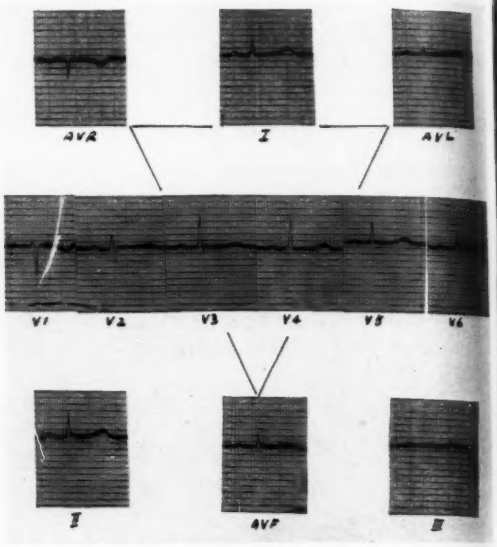

FIG. 4.—Electrocardiogram of same patient as Fig. 2 after pneumoperitoneum. Note deep Q3 with flat T. aVL shows taller R than before PP due to shift to the left. V2 shows R=S due to counter-clockwise rotation.

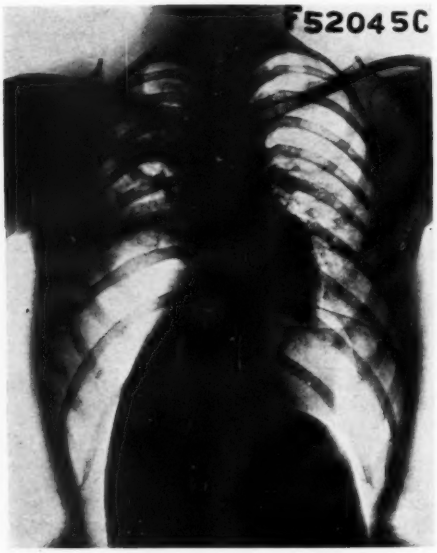

FIG. 5.—X-ray picture of same patient as in Fig. 1 after pneumoperitoneum + Right phrenic crush.

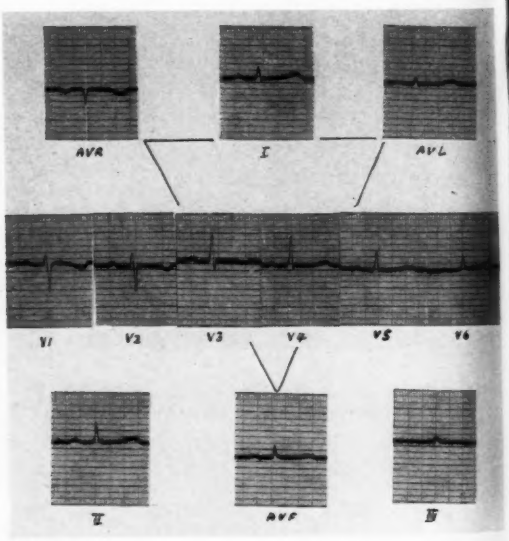

FIG. 6.—Electrocardiogram of same patient as in Fig. 2 after pneumoperitoneum+right phrenic crush. Note Q3; V2 again shows S>R due to clockwise rotation.

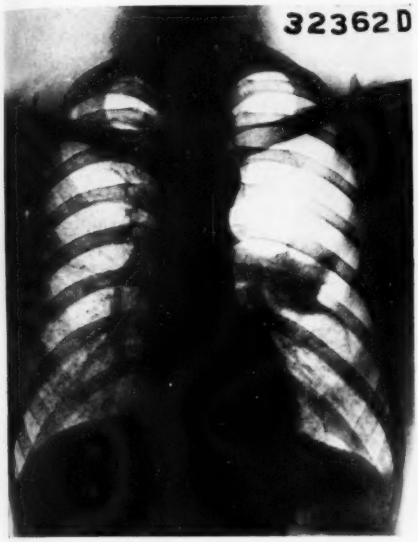

FIG. 7.—X-ray picture, showing artificial pneumothorax (left).

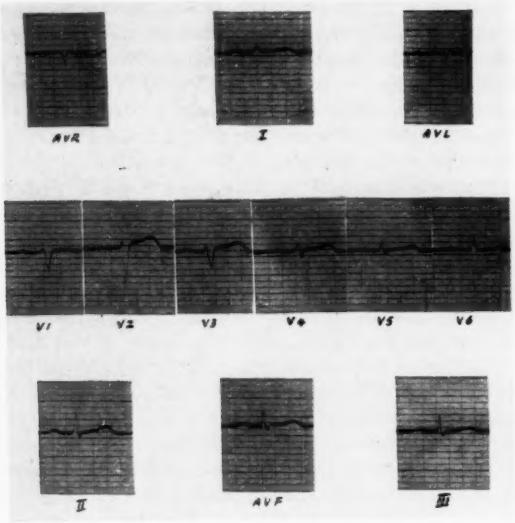

FIG. 8.—Electrocardiogram taken while the patient was having artificial pneumothorax (left.) AVL and I show low R; V4 shows R=S.

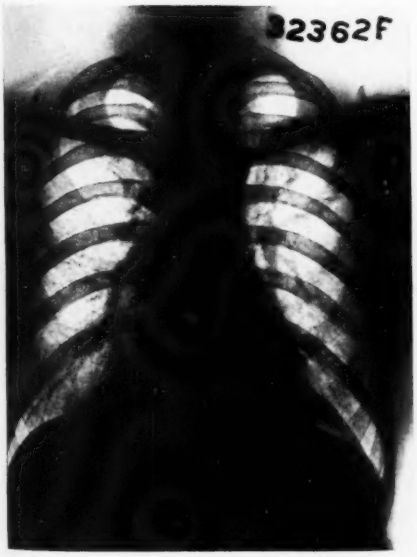

FIG. 9.—X-ray picture of same patient as in Fig. 7, showing the left lung re-expanded.

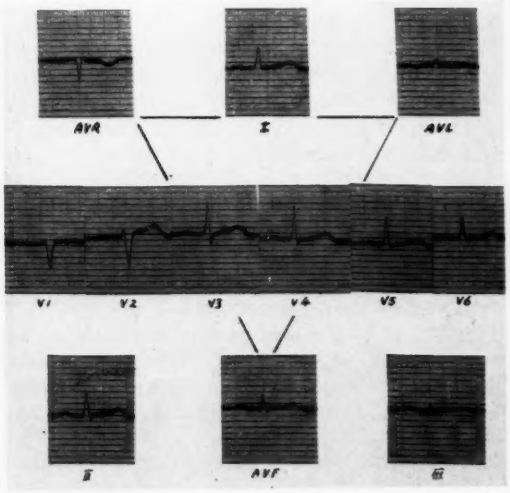

FIG. 10.—Electrocardiogram of same patient as in Fig. 8 after re-expansion of lung. AVL and I show taller R due to a shift to the left; V4 shows R much greater than S due to counter-clockwise rotation. Discontinuation of artificial pneumothorax and re-expansion of lung caused a shift to the left and counter-clockwise rotation.

even when full of air. The direct effect of a right-sided pneumothorax would be to displace the apex to the left, but the displacement of the heart to the left is much less than the compression of the right lung as seen in the skiagrams when the right lung is well collapsed by artificial pneumothorax. This is partly due to the fact that the lung, the right lung in this instance, is more compressible than the heart is moveable, and partly to the fact that the left lung and the semi-rigid thoracic wall on the left side offer a resistance to the movement of the heart towards the left. The heart is usually pointing forwards and so the force exerted by a right-sided pneumothorax which pushes the heart to the left, when it meets with resistance, will make the heart rotate forward, i.e. in a counter-clockwise rotation, so that a shift of the heart to the left will be automatically followed by counter-clockwise rotation (Meek and Wilson, 1925). In a left-sided pneumothorax the reverse changes will follow, but as shown above the displacement of the heart is much less, because when the heart is pushed to the right the resistance of the right lung, the vertebral column and the sternum make movement difficult, resulting in marked clockwise rotation. Pneumoperitoneum, because of the rise of the diaphragm, causes a shift of the apex to the left, counter-clockwise rotation and forward rotation of the apex, if the apex was originally pointing forwards, and backward rotation if the apex was originally pointing backwards. Right phrenic crush superimposed on a pneumoperitoneum causes a rise of the right dome of the diaphragm. This causes an increase in the transverse diameter of the right auricle, displacement of the apex to the right, which in turn, is followed by clockwise rotation, and backward rotation of the apex. Left phrenic crush will cause the same result as pneumoperitoneum, and if pneumoperitoneum has already been performed, the results will be accentuated. Further, the interposition of air between the heart and the electrode may cause a lowered voltage in the lead concerned so that lowered voltage may be expected in some of the air-introducing procedures, particularly in left-sided artificial pneumothorax as the air then envelopes the heart on three sides.

The main electrocardiographic changes produced can be accounted for on mechanical grounds.

(1) Pneumoperitoneum. A shift to the left would account for an increased R in aVL and I, counter-clockwise rotation for an increased R in V2, V3, and V4, and interposition of air between the heart and the electrode for decreased R in aVF and II.

(2) Pneumoperitoneum and right phrenic crush. An increased R in I, V2, and V4, and a decreased R in II, III, and aVF can be explained as in (1) above.

(3) Right phrenic crush. A decreased R in V3 and V4 and an increased S in V2 could result from clockwise rotation.

(4) Right-sided artificial pneumothorax. An increased R in V4 and V5 could result from counter-clockwise rotation.

(5) Left-sided artificial pneumothorax. A decreased R in I, V4, and V6 could result from a shift to the right and clockwise rotation or low voltage due to the interposition of air between the heart and the electrode.

(6) Pneumoperitoneum and left phrenic crush. A shift to the left would account for an increased R in aVL and I and counter-clockwise rotation for an increased R in V2, V3, and V4 and a decreased S in V1.

(7) Left phrenic crush. A shift to the left would account for an increased RI and the interposition of air between the heart and the electrode for a decreased R in V4 and V6.

An attempt will now be made to analyse previous work in the light of the above hypothesis. Master (1928) found S–T deviation, right axis deviation, low voltage and TIII inversion in pneumothorax. Case 1 (right pneumothorax) showed S–T abnormality and large amplitude of QRS in lead III. There was right ventricular hypertrophy and failure as shown by the forceful apex beat and the enlarged liver in his cases, which would account for right axis deviation and the S–T deviation; the large QRS in III is explained by the fact that the air in right-sided pneumothorax is interposed between the two electrodes of I and II but not III which is connected to the left leg and left arm. Case 2 after right-sided artificial pneumothorax showed low voltage in all three standard

limb leads and flat TIII. The low voltage in I and II was due to the interposition of air between the electrodes and in lead III both the low QRS and flat T were due to the fact that the apex had shifted to the left causing R and T to become taller in aVL, which would in turn cause QRS and T to be lower in III. The above explanation would probably hold for the other cases which are not reported in detail. Benatt and Berg (1945) found that artificial pneumoperitoneum produced a QTIII pattern and a flattening of S–TII. The QTIII is due to the fact that pneumoperitoneum causes a shift of the apex to the left, giving rise to a taller R and a taller T in aVL. The S–T flattening is only an impression created by the lowering of the T wave. Littmann (1946) found absence of R waves and presence of inverted T waves in CF2 and CF3 in the supine position only, in spontaneous pneumothorax complicated by mediastinal emphysema. On studying the cardiograms of the first case reported in this paper, it is found that CF2 and CF3 have inverted P waves, QS and inverted T, i.e. the pattern that is normally seen in V1; lead CF1 is not recorded nor are the V leads. The explanation may be as follows: due to the left pneumothorax the heart is shifted to the right ; such a shift is always accompanied by clockwise rotation, which would result in V2 and V3 recording similar patterns to V1. Now CF2 and CF3 really equal V2–VF and V3–VF respectively. In the supine position the air in the mediastinum would accumulate anterior to the heart and cause backward rotation of the apex so that the leg would face the epicardial surface of the right ventricle and give an rS complex of low voltage due to the fact that air is a poor conductor —this would not affect the form of the resultant complex which would therefore be similar to V1.

Armen and Frank (1949) investigated 45 cases of pneumothorax and found, in right-sided artificial pneumothorax, depression of QRS1 (8 out of 20 cases), depression of P waves (11 out of 20 cases), and depression or flattening of T1 (10 out of 20 cases). The depression of QRS1 can be due to the fact that the negativity of VR is lessened due to low voltage, the depression of P waves to low voltage, and the depressed T1 follows the depression of QRS1. In left-sided artificial pneumothorax they found low voltage of QRS1, depression of P1, depression of T1 and inversion of T in CF2, CF4, and CF5. It is quite obvious that all these changes can result from lowered voltage. There was no S–T elevation or depression in any of the cases. The findings of Rauchwerger and Erskine (1949) and of Silverberg and Feldman (1950) in chest surgery are not easy to explain. In any case chest surgery cannot be expected to produce uncomplicated positional change of the heart as many other factors are involved, e.g. the presence or absence of segmental or lobar collapse, bronchiectasis, fibrosis of the lung and effusion.

Evans and Black (1950) investigating 10 cases of artificial pneumoperitoneum found abnormally large Q waves in the œsophageal leads and have explained this change as resulting from forward displacement of the apex. Pollak (1951) investigated 19 cases of pneumoperitoneum and found that no significant changes resulted in the recumbent position; in the sitting position, however, QIII was found in 4, TIII in 13, and left axis deviation in 9 cases. When a normal person sits up the diaphragm descends due to the " falling away " of the abdominal contents, and quite independently, the heart assumes a more vertical position. In the presence of pneumoperitoneum, however, the diaphragm will not descend as much as usual because of the presence of air underneath it but the force of gravity will make the heart try to assume a more vertical position, therefore the apex will shift to the left and counter-clockwise rotation occur. VL will show taller R and T; this accounts for QTIII and left axis deviation. Weinshel *et al.* (1951) found that, after right pneumothorax the electrical position of the heart became more vertical and the transition zone shifted to the left in 5 out of 9 cases; it is not possible to explain this without more data. In left pneumothorax the amplitude of the QRS deflection in the præcordial leads was diminished; this was due to low voltage resulting from interposition of air between the heart and the electrode. Pneumoperitoneum caused a shift to the left and counter-clockwise rotation as expected. Weiss (1951) in a study of 10 cases of pneumoperitoneum and pneumonectomy thought that the therapeutic measures themselves had little effect on the electrocardiogram, but that the changes found were the result of subclinical cor pulmonale; these findings are not borne out by the present study. Rubin and Most (1952) studying 12 patients with pneumoperitoneum found that 7 cases developed deep Q waves

in the œsophageal leads; this is due to forward rotation of the apex and upward displacement of the heart so that the œsophageal electrode would be placed below the level of the heart.

It will be seen that in most cases an explanation is possible on the hypothesis that has been put forward. A full explanation cannot be expected in the absence of complete data in each case including a twelve-lead electrocardiographic study before and after the carrying out of the therapeutic measure and this is not available in many of the previous publications.

Summary

A number of cases were studied electrocardiographically before and after undergoing pneumoperitoneum, artificial pneumothorax, or phrenic crush.

It is submitted that the main changes were the result of the mechanical effects produced by the therapeutic procedure employed.

I have to thank the patients for their co-operation, Dr. W. J. Vickers, the Director Medical Services, Singapore, for allowing me to take electrocardiograms of patients at Tan Tock Seng Hospital, Dr. R. J. Grove-White for his valuable assistance in the collection of data at Tan Tock Seng Hospital, the X-Ray Departments of the General Hospital, Tan Tock Seng Hospital and of the Singapore Anti-Tuberculosis Association for the skiagrams, and Miss Lim Kim Chwee for having taken the electrocardiograms.

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RADIOLOGY OF THE LUNG IN LEFT HEART FAILURE

BY

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James Hope (1839) was probably the first to recognize that engorgement of the lungs was the cause of cardiac asthma. For almost a century, students were taught to seek for basal rales and signs of hydrothorax as evidence of such engorgement. During the past 30 years, however, as a result of the pioneer work of Laubry *et al.* (1929), Zdansky (1929, 1933), Kerley (1933), Parkinson (1933), and Roesler (1937), the superiority of radiological over clinical examination in this field has become recognized. Further advances in the radiology of the lung in heart disease have been made by Bedford and Lovibond (1941), Donzelot and Heim de Balsac (1947), and Jackson (1951).

Recent progress in radiological technique has greatly facilitated the study of the lung fields. It is opportune, therefore, to re-examine the changes that take place in heart disease. A previous study (Short, 1955) dealt with the pulmonary changes in severe mitral stenosis. The present investigation is concerned with the lung pattern in left heart failure.

METHODS

A consecutive series of patients undergoing investigation on account of left heart failure or left ventricular enlargement were examined radiographically. Patients were omitted from the series if there was evidence of organic disease of the mitral valve or lung parenchyma, or if the radiograph was unsatisfactory. Patients with emphysema were therefore excluded, but not those with bronchitis alone. The criteria of a satisfactory film were those laid down by the Medical Research Council X-ray Subcommittee.

Of the 51 patients admitted to the series, 31 suffered from hypertension with or without cardiac infarction; in five cases, the hypertension was of the malignant variety and in one it was due to chronic nephritis. Five had cardiac infarction without hypertension, three had left bundle-branch block of undetermined ætiology and twelve had aortic valve disease. In one, without evident heart disease, left heart failure developed during a prolonged attack of auricular tachycardia. The ages of the patients ranged from 20 to 72, four-fifths being between 40 and 70 years old.

A full history was recorded in each case, particular attention being paid to symptoms suggestive of heart failure. In the clinical examination, special note was made of the presence of triple heart rhythm and signs of venous engorgement. Each patient had at least one electrocardiogram. One patient was in established auricular fibrillation, two suffered from paroxysmal auricular fibrillation, and one from paroxysmal auricular tachycardia. The remainder were in sinus rhythm.

Thirty-four patients were observed in 43 episodes of clinical heart failure and, either during the course of failure or subsequently, 63 radiographic examinations were made. Thirty-four radiograms were taken in the presence of heart failure, 21 within a month of the subsidence of failure, and 8 more than two months after. In 19 episodes, paroxysmal dyspnœa was the dominant symptom. Four episodes were marked by persistent orthopnœa, five by dyspnœa on exertion only, and sixteen were associated with right heart failure, as shown by jugular venous engorgement or hepatic enlargement accompanied by œdema.

Fifteen patients were observed in 17 episodes of doubtful heart failure in the course of which 19 radiograms were taken. The doubt generally arose over a history of dyspnœa occurring only on exertion or attacks simulating cardiac asthma. In three patients clinical evidence of failure appeared later.

* Part of this work was done while holding a Leverhulme Research Scholarship.

Nine patients without clinical evidence of heart failure were examined radiographically, two of them twice. Four later developed failure.

Each radiographic examination was performed in the X-ray department and consisted of a postero-anterior film taken with a tube-film distance of six feet, at 300 mA, approximately 65 kV and 1/10 second exposure. A left lateral film was exposed in most instances, and often a right lateral also. Ward films were not requested and thus no attempt was made to follow in detail the resolution of pulmonary congestion.

The films were examined without knowledge of the history and clinical findings, particular attention being paid to the size of the pulmonary trunk, its main and its intra-pulmonary branches, the size of the pulmonary veins, the presence of hilar and pulmonary clouding, thickening or duplication of the lung fissures, and hydrothorax. The parenchymal pattern was scrutinized for interlobular lines and other abnormalities (Fig. 1).

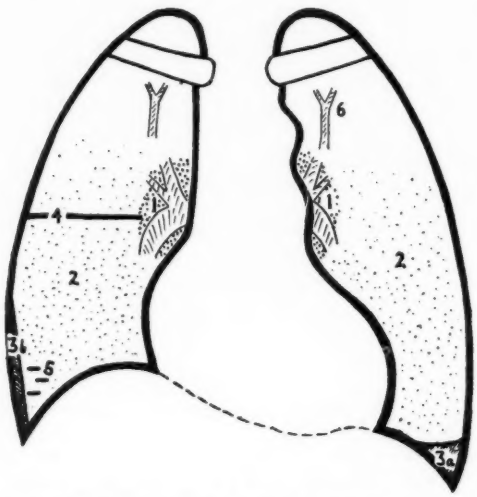


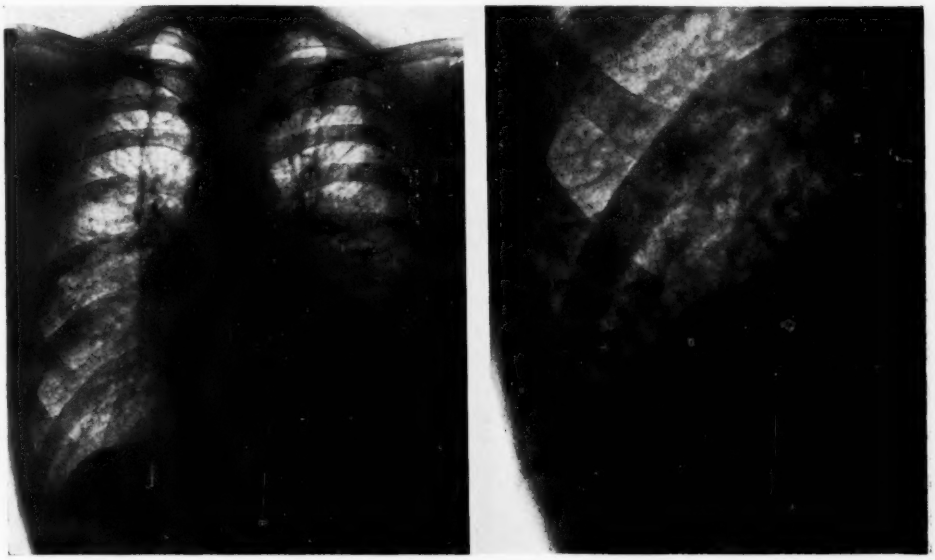
FIG. 1.—*Pulmonary congestion in left heart failure.* (1) Hilar clouding; (2) Pulmonary clouding; (3) Hydrothorax, (*a*) costo-phrenic, (*b*) lamellar; (4) Interlobar line; (5) Interlobular lines; (6) Venous distension.

One of the greatest difficulties in radiographic interpretation is to determine the bounds of normality. This applies to pulmonary and especially to hilar clouding, the recognition of which leads to frequent disagreement even amongst experienced observers. Indeed, Laubry *et al.* (1939) have stated that the individual variability of the hilum and the anatomical and vaso-motor state of pulmonary arteries rendered the appreciation of venous stasis impossible at the outset. Advances in technique, while they have reduced the difficulty, have not eliminated it. In the present study, the dividing line has been drawn in such a way that few normal hila might be classed as abnormal though some abnormal ones might be classed as normal.

Hilar clouding, hydrothorax, interlobular lines, and indeed each feature of pulmonary congestion may be simulated more or less closely by non-cardiac diseases, so it is important to consider the lung changes in heart failure not only in detail but also as a composite picture.

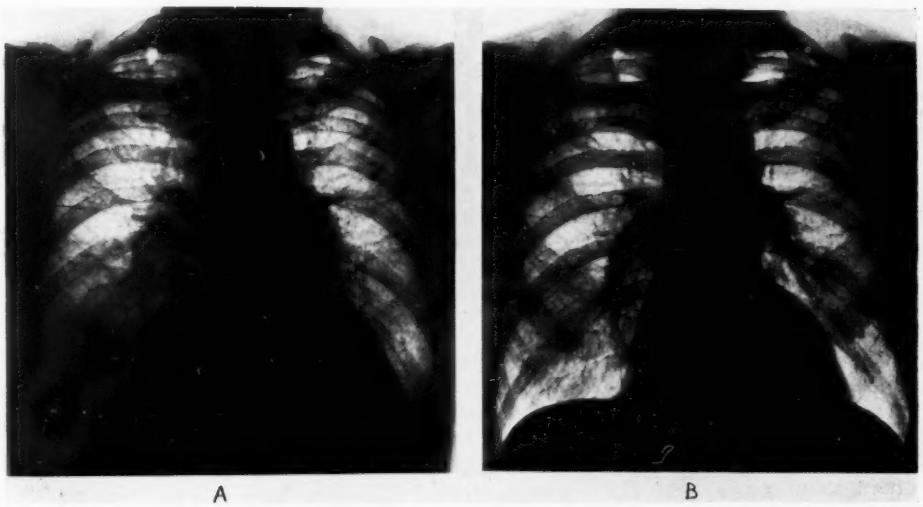
RESULTS

An abnormal lung pattern was observed in 67 radiograms from 39 patients. The commonest abnormality was hilar clouding. The margins of the pulmonary arteries and their lobar branches were veiled, and the lumen of the right bronchus obscured, in 61 instances. Hilar clouding was moderate in 46 instances and considerable or great in 15 (Fig. 2 and 3).



A B

FIG. 2.—Left heart failure due to aortic stenosis. (A) Full chest. (B) Contact print of right lower zone.
Note.—Hilar and pulmonary clouding, and interlobular lines in the right costophrenic angle.

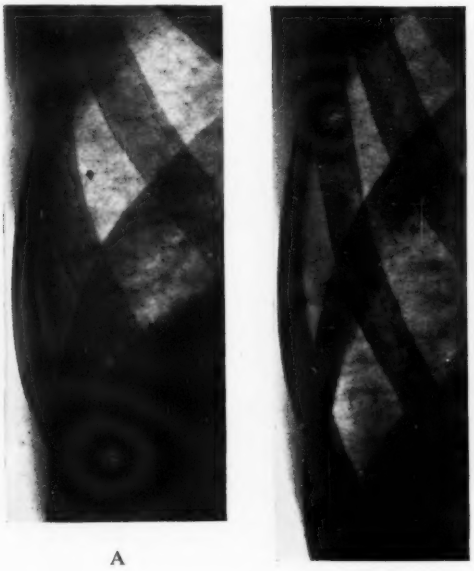


A B

FIG. 3.—Biventricular failure due to hypertension. (A) At the height of failure, showing hilar clouding, interlobar line, and bilateral hydrothorax. (B) Three weeks later, showing almost complete resolution.

Involvement of the pleura was the next most frequent finding, being observed in 51 films. Hydrothorax was present in 29 and widening of the horizontal or oblique fissures (Fig. 3) in the remainder. The amount of fluid varied from an effusion covering three-quarters of the hemi-thorax to a mere trace in the costophrenic sulcus, perhaps visible only in the lateral projection, or a small lamellar collection. The latter, consisting of a thin layer of fluid overlying the costal surface of the lung and visible only in a tangential projection, was seen in 4 patients. In three, the underlying lung was marked by interlobular lines (Fig. 4). The hydrothorax was bilateral in 17, right-sided in 10 and left-sided in 2 instances. Where it was bilateral the larger collection was frequently left-sided. Thus in nine cases, the greater amount was on the left, in four cases on the right, while in four, the two effusions were approximately equal.

Examination of the clinical notes of the patients with hydrothorax showed that 13 were in isolated left heart failure and 16 in biventricular failure. There was no significant difference in the localization of the effusions in the two groups.



A B

FIG. 4.—Right costophrenic angle of a patient with malignant hypertension. (A) In failure, showing lamellar effusion and faint interlobular lines. (B) Two weeks later, showing effusion absorbed. The diaphragm is at a lower level in B.

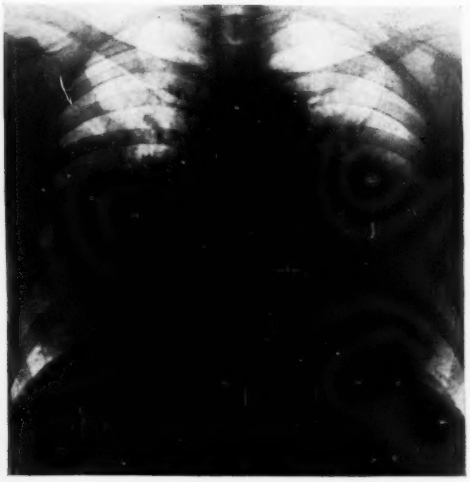


FIG. 5.—Pulmonary œdema in a patient with malignant hypertension.

The lung translucency was reduced, particularly in the lower half, with consequent loss of definition of the ribs, heart, and pulmonary vessels in 40 films. Pulmonary clouding was generally moderate in degree and only twice did the appearance indicate frank pulmonary œdema. Once both lungs were occupied by rather discrete, spherical clouds 1–2 cm. in diameter (Fig. 5). In the second case, long streaks radiated out from the hilum like the spokes of a wheel. Widening of the oblique fissures frequently contributed to the opacity. An appearance suggesting hæmosiderosis was never seen.

Short horizontal lines were seen in the costophrenic angles in 20 films and in 10 were associated with a small effusion (Fig. 2 and 4). They were similar in appearance to the lines encountered in severe mitral stenosis (Short, 1955), though neither so numerous nor, as a rule, so sharply defined

as in that condition. These lines, first described by Kerley (1933), correspond to the interlobular septa. I have previously referred to them as septal lines but the term interlobular lines seems preferable.

Enlargement of the pulmonary trunk was observed in 13 radiograms and once the enlargement extended into the main branches (Fig. 3). The intrapulmonary arteries were frequently obscured, especially in the lower half of the lung, but when visible, their calibre was within normal limits. Pulmonary veins were often recognized in the upper lobes, but venous distension was conclusively demonstrated only eight times.

Clinical assessment, made independently of the radiological study, indicated present or past heart failure corresponding to 58 of the 67 films reported as abnormal. In 32 instances clinical signs of heart failure were present at the time of X-ray examination, in 19 failure had recently subsided, and 2 to 16 months had elapsed since the last episode or failure in 7 cases.

Radiograms demonstrated the presence of pulmonary congestion in one patient whose symptoms suggested isolated right heart failure.

A man, aged 67, suffering from cardiac infarction and left bundle branch-block developed swelling of the scrotum followed shortly by œdema of the legs. Dyspnœa on exertion was minimal. All signs of systemic venous congestion had subsided when he attended hospital for examination; the third heart sound was, however, audible. The radiogram showed moderate enlargement of the left ventricle, right atrium, and pulmonary artery, considerable hilar clouding, and widening of the horizontal and oblique fissures.

Pulmonary congestion was demonstrated in seven patients in whom the existence of heart failure was uncertain after careful clinical examination. Each patient denied paroxysmal dyspnœa, whether occurring spontaneously or following exertion, and admitted to only slight dyspnœa on effort. Clinical evidence of right heart failure was absent and a third heart sound was heard twice only. The following two cases illustrate this point.

A man, aged 37, with a blood pressure of 250/130 was anxious over a past syphilitic infection. He was admitted to hospital for lumbar puncture and chest X-Ray to exclude syphilitic disease of the central nervous system and aorta. In response to detailed questioning he admitted being breathless after climbing about ten stairs but said he could walk any distance on the flat. He had never been orthopnœic except once during a fog when he developed a cough. There were no signs of venous engorgement and there was no triple heart rhythm. In view of the obvious anxiety neurosis the breathlessness was discounted, and when the X-ray showed the aorta to be normal, the patient was discharged with reassurance. Inspection of the lung fields, however, showed clear evidence of pulmonary congestion, namely, hilar and pulmonary clouding, widening of the horizontal fissure, a lamellar effusion and interlobular lines. Eight months later, the patient returned with great dyspnœa and signs of venous engorgement. He had passed the stage of isolated left heart failure and entered that of biventricular failure.

A man, aged 64, suffering from syphilitic aortic incompetence and auricular fibrillation had been taking digitalis regularly for four years. Though there was considerable cardiac enlargement he had never been in failure. When he attended for routine surveillance of his syphilitic lesion, he made no complaint of dyspnœa. A radiographic examination was requested in order to determine the size of the aorta. This was found to be satisfactory, and since failure was not suspected, the patient was reassured. Later, when attention was directed to the lung fields, the presence of pulmonary congestion was evident for there was hilar and pulmonary clouding, a lamellar effusion and interlobular lines. When he next attended hospital three months later, he was complaining of paroxysmal nocturnal dyspnœa and the recent appearance of dropsy.

Fourteen patients, whose initial radiographic examination was made while in heart failure were subsequently re-examined on one or more occasions. In one patient, two episodes of heart failure were followed in this way. In nine instances, the interval between the first and second examinations was 10 to 18 days, in four 22 to 30 days, in one two months and in another nine months.

In four instances, where there was no amelioration in the patient's condition, the radiogram showed no improvement. Effusions persisted or even increased despite some decline in hilar and pulmonary clouding in two cases. In three instances, where there was moderate improvement,

the film showed some, though incomplete resolution. Hilar and pulmonary clouding receded, but twice a small hydrothorax and once interlobular lines persisted.

In eight instances where clinical signs of failure cleared rapidly, the radiographic improvement was also striking (Fig. 3). Within 10 to 21 days, large effusions vanished, pleural thickening subsided, lung translucency returned to normal, and interlobular lines disappeared. Hilar clouding invariably decreased, though only twice did it disappear altogether. Once was in a patient whose heart appeared healthy and in whom heart failure was precipitated by tachycardia. The other was in a patient with hypertensive heart failure whose clinical recovery was remarkably complete.

In 10 instances, the radiological evidence of pulmonary congestion was equivocal. In six of these, the corresponding clinical examination was also equivocal. In two, there had been previous heart failure, one was believed actually to be in early failure, and the last showed no evidence of heart failure at that time but developed it subsequently.

Seventeen films were normal. Ten related to patients who had never been in heart failure, five to patients in whom the clinical findings were equivocal, and two to patients who had previously suffered from heart failure but had made exceptionally good recoveries.

Discussion

It is rarely practicable or necessary to conduct a radiographic examination during an attack of acute pulmonary œdema. The striking picture of intense pulmonary clouding has, however, been well described by Jackson (1951). If the attack is mild and radiographic examination is postponed for several hours the signs of pulmonary congestion may be slight or altogether absent since resolution is often both rapid and complete.

When left heart failure develops more gradually, the most striking changes in the lung fields are hilar clouding and widening of the interlobar fissures, often accompanied by effusion. Although usually bilateral or right-sided, hydrothorax is often confined to the left side, particularly in the presence of sinus rhythm and isolated left heart failure (Bedford and Lovibond, 1941).

The fact that hydrothorax may occur in isolated left heart failure was first pointed out by Bedford (1939) and is now generally recognized. Hydrothorax is indeed more characteristic of failure of the left than of the right heart. In isolated right heart failure, as in tricuspid valve disease, the infrequency of hydrothorax is in marked contrast to the constancy of ascites and dropsy. In isolated left heart failure, on the other hand, hydrothorax is common. The fact that it is more common when failure of the right heart follows defeat of the left is surely due to the fact that this represents a more advanced stage of left heart failure.

A large hydrothorax is readily detected, but small effusions are easily missed. Fluid in the posterior costophrenic sulcus may be overlooked unless the patient is rotated into the oblique or lateral position. A similar procedure is necessary in order to demonstrate fluid within the oblique fissure.

A lamellar effusion must be distinguished from the intercostal muscles which are sometimes seen tangentially as a straight or slightly convex line when the ribs overlap at a steep angle (Kerley, 1951). The distinction is, as a rule, readily made for the pulmonary surface of an effusion is usually concave, and never convex; moreover the underlying lung is often marked by interlobular lines.

Other changes in the lung fields in subacute and chronic left heart failure include pulmonary clouding with a basal preponderance and interlobular lines. The latter must not be confused with the blood vessels which are sometimes seen in the costophrenic angles in health (Short, 1955). The pulmonary artery trunk is not infrequently enlarged but distension of the veins in the upper lobes is seldom distinctive enough to be helpful.

With the subsidence of failure, pulmonary congestion abates quickly. Within a week or two the parenchyma clears, interlobular lines vanish, hilar clouding recedes, and effusions are absorbed. Nevertheless, resolution is rarely quite complete for, as Evans (1952) has indicated, some hilar clouding generally persists. The precise nature of the structural changes involved in hilar clouding is not yet known, so that the significance of their persistence is uncertain. Undoubtedly, the main

branches of the pulmonary artery may remain dilated or unfolded after recovery and so impart to the hila an abnormal prominence (Fig. 3), but where actual clouding persists, latent heart failure must be considered likely.

Accurate detection of pulmonary congestion is best achieved by a combination of radiography with radioscopy. Radioscopy is eminently suitable for the detection of hilar clouding and pleural effusions. Radiography is superior in the demonstration of parenchymal detail and particularly of interlobular lines.

Where the existence of heart failure is uncertain after a careful clinical examination, a radiogram is frequently conclusive. In the present series, there were 17 episodes in which the clinical evidence was equivocal and doubt was resolved in all but five.

The problem commonly arises in a patient with hypertension who complains of dyspnœa only on effort and admits to none of the other symptoms of left heart failure. Other potential causes of dyspnœa, such as bronchitis or a recent increase in weight, may be evident. Physical examination reveals signs of cardiovascular hypertrophy without venous engorgement or a third heart sound. The electrocardiogram shows the pattern of left ventricular enlargement with normal P waves and cardioscopy shows moderate enlargement of the left ventricle and doubtful hilar clouding.

The diagnosis is not merely of academic interest for, if early heart failure is overlooked, and treatment withheld the patient may next appear in advanced failure as happened to two patients in the present series. If failure is absent, however, such treatment is unnecessary and in some respects harmful. The cause of the dyspnœa should be explained, appropriate measures advised and the patient reassured about the state of his heart. A radiographic examination is a most helpful guide to the presence of left heart failure. The demonstration of pulmonary congestion indicates failure, while its absence excludes it. There is inevitably a borderline group in which doubt remains, but it is small.

The fact that unequivocal evidence of pulmonary congestion is sometimes found in patients with very slight symptoms suggests that it may occasionally be possible to diagnose left heart failure before the appearance of any symptoms. This view is supported by the observation that hæmodynamic and anatomical changes in the lesser circulation precede symptoms.

Failure of the left ventricle leads to a rise in pressure, primarily in the left atrium, and secondarily in the pulmonary artery. In well marked left heart failure, right ventricular hypertrophy is a constant finding at necropsy (Traube, 1856), and catheterization studies have shown that pulmonary hypertension may be as severe as in mitral stenosis (Lenegre and Maurice, 1947; Lewis *et al.*, 1953). Hypertrophy of the right ventricle (Thompson and White, 1936) and of the muscular arteries of the lung (Smith *et al.*, 1954) are, however, sometimes found at necropsy in patients with systemic hypertension or aortic valve disease who showed no clinical evidence of heart failure and pulmonary hypertension has occasionally been demonstrated in similar groups of patients, even at rest.

Radiological evidence of pulmonary congestion should therefore be sought in all patients with severe hypertension, aortic valve disease, or cardiac infarction, even in the absence of any complaint of dyspnœa. Radiography following exercise may prove an even more sensitive test of left ventricular competence than the standard radiogram at rest.

The pattern of pulmonary congestion in left heart failure differs from that found in mitral stenosis (Short, 1955) in two important respects. In mitral stenosis, hydrothorax is infrequent and usually unilateral, whereas in left heart failure hydrothorax is common and generally bilateral. In mitral stenosis, the pulmonary changes are persistent and progressive, whereas in left heart failure they are, for the most part, transient.

There are other less striking differences between the two groups. In mitral stenosis, the boundary of the hilum is usually sharp, loss of translucency is associated with increased parenchymal detail, and hæmosiderosis is not uncommon. In left heart failure, on the other hand, the margin of the hilum is frequently blurred, parenchymal detail tends to be clouded, and hæmosiderosis is very rare. Interlobular lines are found in a high proportion of patients with severe mitral stenosis;

they are sharply defined and frequently profuse. In left heart failure the lines are less common, less sharply defined, scanty and often associated with a small hydrothorax. In mitral stenosis the enlargement of the pulmonary trunk tends to be greater than that of its branches, whereas in left heart failure, the reverse is true.

The distinctive radiological patterns of left heart failure and mitral stenosis reflect basic hæmodynamic and pathological differences between the two diseases. One is the response of the lung to a labile pulmonary venous pressure, the other, to a persistently elevated and slowly rising pressure. One is engorgement, the other induration.

Recognition of these patterns should prove helpful in the diagnosis of rheumatic heart disease. In a patient with both mitral and aortic stenosis, for example, a mitral pattern would indicate that mitral stenosis was the dominant lesion, whereas a heart failure pattern would indicate that the aortic lesion was dominant. Similarly, in a patient in whom the mitral valve only was affected, a heart failure pattern would point to some complicating factor such as advanced myocardial disease or an important degree of mitral incompetence.

Summary

Ninety-three radiographic examinations were made on 51 patients with left heart failure or left ventricular enlargement.

Forty-three episodes of clinical heart failure were studied, distinctive abnormalities being demonstrated in all but one. Hilar clouding and widening of the lung fissures, with or without hydrothorax, were the most frequent findings; pulmonary clouding and interlobular lines were less constant.

There were 17 episodes in which a diagnosis of heart failure was uncertain after careful clinical examination. Doubt was resolved by radiography in all save five, pulmonary congestion being demonstrated in seven and a normal lung architecture in five.

Pulmonary congestion was demonstrated in several patients who were almost free of symptoms. In two instances where the significance of the radiological signs was overlooked, advanced heart failure developed within a few months.

The pattern of pulmonary congestion in left heart failure is contrasted with that in severe mitral stenosis, and the application of this knowledge to the diagnosis of rheumatic heart disease is indicated.

I am indebted to Dr. William Evans, Dr. Evan Bedford, and Dr. Wallace Brigden under whose care these patients were admitted to hospital, and also to Dr. Peter Kerley, for much helpful criticism. I also acknowledge the ready co-operation of the Radiological Departments at both hospitals.

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THE PATTERN OF RESPIRATION IN RHEUMATIC HEART DISEASE

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It is well known that the earliest symptom of mitral stenosis is shortness of breath with moderate exertion (Baker, Brock, Campbell, and Wood, 1952). However, the relationship between this sensation of dyspnœa and departures from the normal pattern of respiratory function is less clearly defined.

It has been shown recently (Shephard, 1955*a*) that in congenital heart cases there is a relationship that is highly significant statistically between the level of pulmonary flow and the depth of respiration. This finding was explained by postulating an associated alteration in the elastic properties of the lungs. With an increase of pulmonary blood flow it was suggested there was an increased resistance to distension, leading to the adoption of a shallow and inefficient pattern of respiration. There is some evidence that a similar change occurs with the pulmonary congestion of mitral stenosis and other forms of rheumatic heart disease. It was shown many years ago (Campbell, Hunt, and Poulton, 1923; Campbell and Sale, 1927) that patients with mitral stenosis tended to develop a rapid, shallow pattern of respiration, and calculations of the work of breathing (Christie and Meakins, 1934; Christie, 1953) have given support to this concept of respiratory inefficiency.

The present paper reports our findings in a group of 116 patients with rheumatic heart disease (55 with pure mitral stenosis, and 61 with other valvular lesions). The pattern of respiration before and during moderate exercise is examined, and compared with the degree of disability (based on history, see Baker *et al.*, 1952) and hæmodynamic measurements made at cardiac catheterization. The problem of dyspnœa is discussed, and an analysis made of the factors contributing to this symptom in rheumatic heart disease.

METHODS

The Patients. Cases were unselected patients presented for cardiac catheterization but a small number were omitted from the analysis owing to lack of co-operation, or a disturbed emotional state (as shown by a high metabolic rate). A light breakfast was given three hours before the tests, and at a suitable interval phenobarbitone (1½–2 grains) or amytobarbitone (3 grains). On this regime, most patients seemed close to a basal state, the average metabolic rate for the group being +5·9 per cent. The age, sex distribution, and degree of disability of the cases are summarized in Table I, and for purposes of analysis, the patients have been divided into eight groups.

Technique of Catheterization. The basic technique has been reported by Holling and Zak (1950). Simultaneous pulmonary arterial and capillary tracings are now obtained via a Cournand double-lumen catheter. Pressures are recorded by a twin-channel Southern Instruments capacitance manometer, and Brush direct-writing galvanometers. The oxygen content of blood samples has been determined by the Haldane technique, and more recently by a Beckmann spectrophotometer (Nahas, 1950; Holling *et al.*, 1955).

Respiratory measurements were made by the box-bag technique (Donald and Christie, 1949), the patient lying on a couch with the back supported at an angle of 45 degrees. This angulation was adopted as a routine as a number of the patients showed orthopnœa. A number of control observations were made on students under the same experimental conditions. Vital capacity and supplemental air measurements

TABLE I
AGE, SEX, AND DISABILITY OF CASES

	Mitral stenosis alone				All other rheumatic valve lesions with or without mitral stenosis			
	Normal rhythm		Fibrillating		Normal rhythm		Fibrillating	
	Men	Women	Men	Women	Men	Women	Men	Women
Number of cases	10	30	10	5	4	15	11	31
Average age of group	34·6	33·7	37·6	38·0	38·3	35·7	42·1	38·5
Disability with standard error	3·0 ±0·3	2·5 ±0·2	2·9 ±0·2	2·3 ±0·5	3·5 ±0·3	2·7 ±0·3	3·1 ±0·1	3·4 ±0·2

represent the best of three successive estimations. Exercise was provided by a standard pedalling test (described elsewhere: Holling and Venner, 1955), and respiratory measurements were repeated during the fourth minute of this test.

Measures of Disability. The available measures of cardiac dysfunction comprise the clinical grading and hæmodynamic measurements—the pulmonary arterial and pulmonary capillary pressures and the pulmonary flow. Before attempting to correlate respiratory changes with these values, the practical limitations of each must be considered.

The clinical grading is often used for the construction of graphs—sometimes even the logarithm of the clinical grading is pressed into service. However, it is unlikely that a series of clinical grades will bear any close relation to a normal numerical sequence, and mathematical manipulations with such gradings should therefore be used with caution.

The pulmonary arterial pressure has a definite numerical value, but there is a possibility that the higher pressures sometimes serve a protective function (Lewis *et al.*, 1952) and are not related simply to " back-pressure " effects from stenosis at the mitral valve.

Since an increased capillary blood content and an interstitial œdema are generally considered responsible for the rigidity of the lungs in chronic heart disease, the pulmonary capillary pressure might seem the ideal figure to relate to respiratory changes. In practice, it is difficult to measure, and even when satisfactory tracings are obtained by the wedge technique, the pressure recorded bears no certain relationship to the true capillary pressure. Finally, with increase of disability, pulmonary capillary pressure soon reaches a limiting value (Lewis *et al.*, 1952). The resting pulmonary blood flow is not much reduced in rheumatic heart disease, and bears little relationship to the clinical disability (Holling and Venner, 1956).

The above difficulties are not sufficient to prevent the successful use of hæmodynamic measurements in clinical assessment (Holling and Venner, 1956), but they do limit the possibility of establishing clear correlations between these measurements and changes in the pattern of respiration.

THE PATTERN OF RESTING RESPIRATION

Respiratory Minute Volume. The usually accepted minute volume for adult subjects is 4·01./sq.m./min. B.T.P.S. (Shephard, 1954), and the value of 4·12±0·30 1./sq.m./min. found for six control subjects corresponds closely with this standard. The patients with rheumatic heart disease all show a minute volume slightly greater than normal (Table II). An increase of this order could be due to greater anxiety on the part of the patients, but recent figures published by Wade *et al.* (1953) show a similar trend, with a tendency to decrease of ventilatory volume following valvotomy. The increase of ventilation does not show any correlation with clinical disability or the pulmonary vascular measurements discussed above.

Respiratory Rate. The average respiratory rate (Table II) is very little above the value of 15·3 ±0·9 found for the normal control subjects. This would seem to imply that in this group of patients, the elastic work of resting respiration is not greatly different from normal, since with increased elastic work a higher frequency of respiration is adopted (Fenn, 1951; Christie, 1953).

TABLE II

PATTERN OF RESTING RESPIRATION IN RHEUMATIC HEART DISEASE WITH THE MEAN AND STANDARD ERROR FOR EACH GROUP OF DATA

	Pure mitral stenosis				Other rheumatic valve lesions				Average for 8 groups
	Normal rhythm		Fibrillating		Normal rhythm		Fibrillating		
	Men	Women	Men	Women	Men	Women	Men	Women	
Minute volume l./m.²/min. (BTPS)	4·5 ±0·3	4·5 ±0·2	4·6 ±0·5	5·2 ±0·4	5·0 ±0·2	4·4 ±0·4	5·0 ±0·3	4·5 ±0·2	4·59 ±0·11
Respiratory rate/min.	14·8 ±1·8	16·5 ±0·6	14·2 ±1·4	17·2 ±1·0	15·8 ±1·0	17·1 ±1·2	16·7 ±1·7	16·5 ±1·0	16·3 ±0·5
Tidal volume ml./m.² (BTPS)	324 ±32	281 ±16	318 ±18	307 ±28	323 ±18	264 ±20	334 ±38	288 ±12	325(M) ±15 282(F) ±9
Vital capacity (ml. ATPS)	2587	2367 ±123	2723 ±220	2550	3013	2071 ±105	2275	1942 ±86	2345 ±76
Tidal volume (percentage of vital capacity)	20·9	21·5 ±2·2	21·5 ±2·8	21·8	18·0	18·3 ±1·8	21·5	23·0 ±1·7	21·2 ±0·9
Expiratory reserve (percentage of vital capacity)	19·8	20·0 ±1·5	22·3 ±2·5	30·9	31·6	25·1 ±1·8	17·7	23·7 ±2·1	23·2 ±1·1

Tidal Volume. There is a significant difference between the sexes with respect to tidal volume (Table II), and it is therefore necessary to compare with controls of the same sex. Such a comparison shows that in the women patients (the larger group), the tidal volume per square metre of body surface is significantly greater than normal ($P<0{\cdot}0001$). No correlation can be shown between this increase of tidal volume and the clinical or hæmodynamic measures of disability; this may be explained by the fact that while the central effects of rheumatic heart disease tend to increase tidal volume by their action on the respiratory centre, this tendency is opposed by the increased rigidity of the lungs.

Vital Capacity. The vital capacity is considerably reduced in all groups (Table II), the corresponding values for normal controls being 4420 ml. (men) and 3345±220 ml. (women). In their classical study of 156 " cardiac " cases, Peabody and Wentworth (1917) reported a reduced vital capacity in patients with dyspnœa, and suggested that the lowest values were obtained in patients with decompensation. Some subsequent workers have supported this view (Richards *et al*, 1951; Halmagyi, 1954). On the other hand Holling and Venner (1956) have suggested that the alterations of vital capacity that can be found in rheumatic heart disease are related more to restricted lives and poor physique than to cardiac status. The present series certainly shows little correlation between clinical grade and vital capacity ($P=0{\cdot}3$). However, it may be significant that all of the 7 cases with a vital capacity of less than 1250 ml./sq.m. have a disability grading of 3 or 4. It is also interesting to note that of the women patients, there is a clear difference ($P<0{\cdot}001$) between the pure mitral stenosis cases (average disability 2·49) and those with added valvular lesions (average disability 3·04).

The vital capacity does not show any correlation with the hæmodynamic measures of disability. This is probably explained once again by the fact that changes of vital capacity are determined largely by secondary factors (physique, œdema, infarcts, changes of cardiac size and pulmonary blood volume); these are dependent more on the behaviour of the patient than on the actual size of the mitral orifice.

Calculating the tidal volume as a percentage of the vital capacity, it can be seen that in most

instances the resting ventilation is over 20 per cent of the vital capacity, as compared with the normal control value of some 12 per cent. It is suggested that a ventilation of some 35–40 per cent of the vital capacity is sufficient to produce the symptoms of dyspnœa (Cournand and Richards, 1941), and if this is so it requires a much smaller relative change of tidal volume to produce dyspnœa in these patients.

Chest Position. The expiratory reserve volume is a little below the value of 26·8 per cent of the vital capacity found in the control cases, this difference being on the border line of statistical significance (P=0·05—0·10). Bearing in mind that the vital capacity is also reduced in rheumatic heart disease, the absolute decrease of expiratory reserve is somewhat larger (350–500 ml.). This change may be due mainly to the increase of residual air that has been noted in pulmonary congestion (Drinker *et al.*, 1922; Mack *et al.*, 1947), but it is possible that an increased viscosity of the lung tissues also has a direct effect on end-tidal position, the lung showing a smaller average distension at the end of a normal expiration.

The Response to Exercise

The amount of exercise performed can be gauged approximately from the change of oxygen consumption. In our normal subjects this averaged 113 per cent of the resting metabolic rate, and it was associated with an increase of 24 per cent in respiratory rate, and 42 per cent in tidal volume giving a 73 per cent increase of minute volume (Fig. 1).

Respiratory Minute Volume. The rheumatic heart cases co-operated less well during the exercise test, and the change of metabolism was only 83 per cent. of the resting level. Despite this, the change of respiratory minute volume tends to be greater than in normal subjects (Table III).

TABLE III

Change of Respiratory Pattern with Exercise with the Mean and Standard Error for Each Group of Patients

	Pure mitral stenosis				Other rheumatic valve lesions				Average for 8 groups
	Normal rhythm		Fibrillating		Normal rhythm		Fibrillating		
	Men	Women	Men	Women	Men	Women	Men	Women	
Change of minute volume*	82·8 ±12·6	83·9	67·5 ±9·1	73·7	67·5 ±16·4	119·3 ±10·5	91·8 ±27·7	71·4 ±5·6	81·9 ±4·9
Change of respiratory rate*	34·0 ±12·9	38·2 ±8·4	14·3 ±6·6	50·0	35·8	53·1 ±10·0	48·8	41·7 7±·0	39·3 ±3·8
Change of tidal volume*	33·5 ±9·0	33·3 ±7·5	49·5 ±12·6	15·7	27·0 ±13·4	44·1 ±10·1	31·2	24·6 ±4·9	32·8 ±3·4

* All these are expressed as percentages of the normal level.

There is a considerable loss of respiratory efficiency in the rheumatic heart cases, and this may be examined simply in terms of the " ventilatory equivalent " for oxygen. In the controls, there is a resting ventilation of 2·84 l./100 ml. of oxygen consumption, and with exercise this " ventilatory equivalent " falls to 2·30. On the other hand the rheumatic patients show little change with exercise, the corresponding " ventilatory equivalent " values being 3·17 and 3·13 l./100 ml. oxygen.

Respiratory Rate and Tidal Volume. The most interesting feature of the response to exercise is the manner of achieving the increase of minute volume (Fig. 1). The change of rate is almost double that observed in normal subjects, while the increase of tidal volume is not greatly different from normal. This is almost certainly a manifestation of the altered elastic properties of the lungs, and it serves to emphasize the point that even where the pattern of resting respiration is normal, moderate exercise may produce sufficient pulmonary congestion to initiate a rapid and inefficient form of ventilation.

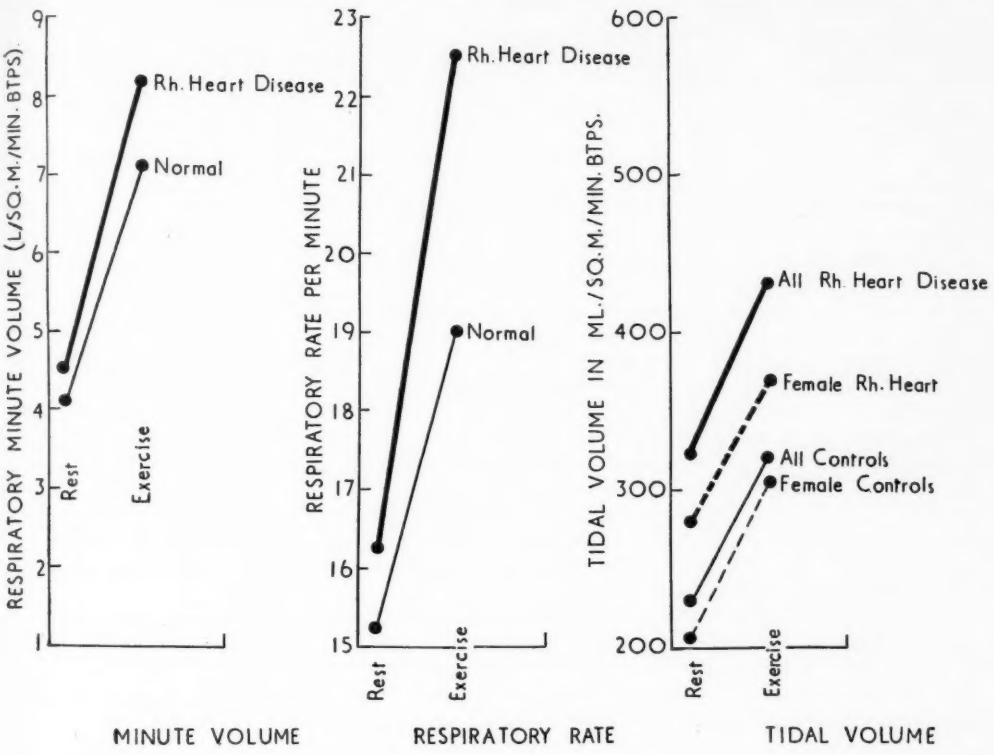

FIG. 1.—The effect of a standard exercise test (Holling and Venner, 1955) on the respiration of normal subjects and a group of 116 cases of rheumatic heart disease. The minute volume is shown on the left, the respiratory rate in the centre, and the tidal volume on the right.

Although the pattern of response to exercise shows a striking departure from normality, it is not possible to establish a correlation between the respiratory rate during exercise and clinical disability or pulmonary vascular measurements. In the case of pulmonary arterial pressure, the explanation may be that the rise of pressure is " protective " in type, and actually limits the change in the pattern of respiration. Again, during exercise, almost all patients are close to the limiting pulmonary capillary pressure of 30 mm. Hg, and a clear correlation of capillary pressure with respiratory changes would not therefore be anticipated. However, the lack of relationship between clinical grading and the respiratory rate during exercise cannot be attributed to extraneous factors. and it implies that an increase of respiratory rate plays little part in the production of dyspnœa.

DISCUSSION

Two factors appear to affect the elasticity of the lungs in rheumatic heart disease—an increase of tissue fluid (" lungenschwellung ") and an increase of pulmonary blood volume (" lungenstarre " effect: Basch 1891). The total capacity of the chest may also be reduced by a variety of factors, including poor physique, an increased pulmonary blood volume, increased heart size, œdema, effusions, and infarcts. Our findings show that at rest the resultant pattern of respiration in the average case of rheumatic heart disease is very close to normal, but that moderate exercise usually

reveals the rapid and shallow pattern of respiration that has been thought typical of mitral stenosis (Campbell *et al.*, 1923; Christie, 1953).

The rather rapid nature of respiration during exercise seems to play a comparatively minor part in the development of dyspnœa. A more important feature is apparently the reduction in vital capacity. Even if the patient is allowed to take his time over the expiration, his capacity is much reduced, and it is probable that during rapid respiration the effective capacity is still smaller owing to the " lungenstarre " effect. The ventilatory efficiency is also reduced and, as a result of these two factors, a comparatively mild amount of exercise is sufficient to reach the dyspnœa threshold. Laboratory evaluation of dyspnœa should therefore be in terms of fast vital capacity and ventilatory efficiency, perhaps in the manner suggested by Stocks and Kennedy (1953), although the E.F.R.[40] value in their equation should preferably be replaced by pooled fast inspiratory and expiratory vital capacity data (Shephard, 1955*b*).

It must be remembered that central carbon dioxide accumulation, psychological influences, and reflex sequelæ of pulmonary congestion may all play some part in reaching the dyspnœa threshold, and these are not assessed by tests of breathing capacity. The general circulation time is increased in mitral stenosis, particularly when the heart is enlarged (Tarr *et al.*, 1933; Cannon *et al.*, 1939; Gübner *et al.*, 1939). Assuming this slowing of the circulation to extend to the cerebral circulation, an abnormal local accumulation of carbon dioxide in the tissues of the respiratory centre might be anticipated, and the relatively normal arterial carbon dioxide content (Campbell *et al.*, 1923) despite recurrent hyperpnœa is in keeping with a situation of this type. Again, many patients have been conditioned to regard themselves as invalids, particularly during childhood and adolescence, and this, together with lack of physical training undoubtedly contributes to the lowered dyspnœa threshold. Finally, pulmonary congestion may exert some action via pulmonary pressure receptors (Bülbring and Whitteridge, 1945).

It seems unlikely that formal laboratory respiratory tests will replace cardiac catheterization in the assessment of rheumatic heart disease, but in the measurement of dyspnœa they should form a useful ancillary to the usual clinical grading. Possibly, simple measurements of respiratory rate or more complicated measurements of the work of breathing may also help increasingly in evaluating the onset of pulmonary congestion during exercise.

Summary

The pattern of respiration has been examined in 116 cases of rheumatic heart disease (55 with pure mitral stenosis and 61 with other valvular lesions) by the box-bag technique. Resting respiration is close to the normal pattern, although there is a slightly greater tidal volume than that found in control cases.

The vital capacity and expiratory reserve are considerably reduced. The decrease of vital capacity shows no clear correlation with disability, or with pulmonary arterial and pulmonary capillary pressures.

With exercise, the ventilation increases more than in normal subjects, and is mechanically less efficient. There is an abnormal increase of respiratory rate, and this forms a useful means of assessing pulmonary congestion.

The symptom of dyspnœa seems related primarily to the reduction of vital capacity, with some contribution from a decreased respiratory efficiency, and laboratory assessment of this symptom should therefore take account of both of these factors.

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TRANSITORY PRÆCORDIAL PULSATION IN CORONARY OCCLUSION

BY

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The diagnostic value of clinical examination by inspection and palpation in organic diseases of the chest has been re-emphasized by Dressler (1937; 1942).

In medical papers of the last three decades, there are only a few scattered references to the development of transitory præcordial pulsations, with or without aneurysm formation, during the acute or early phase of coronary occlusion. Aneurysm formation within one to three weeks of infarction has been reported in the past by Shookhoff and Douglas (1931), White (1945), Caplan and Sherwood (1949), and Vakil (1954). Pulsating aneurysmal bulges that are reversible and last for a few weeks have been reported by Libman and Sacks (1926) and Scherf and Erlsbacher (1934).

As far as can be ascertained no proper enquiry has been undertaken in the past to determine the incidence, characteristics, significance, and outcome of pulsatory phenomena in cases of acute coronary occlusion, and the present study was undertaken to fill in this gap.

Material and Method

Since 1949, 193 cases of acute coronary occlusion have been carefully and repeatedly scrutinized throughout the initial four or five weeks of their illness, for the presence of pulsatory phenomena over the præcordium. Whenever observed, the main characteristics of these pulsations have been recorded and followed up. It has been customary at each examination, first to inspect the præcordial area carefully during the daytime from several different angles; later, the area has been palpated, percussed, and auscultated. In each case, a careful record has been maintained of the clinical history, physical signs, serial electrocardiographic records, routine blood counts, and erythrocyte sedimentation rates.

Of the 193 patients investigated, 172 were men and 21 women. Electrocardiographically, the

TABLE I

Distribution of Cases According to Site of Infarction

	All types	Antero-septal	Extensive anterior	Localized anterior	Posterior	Antero-posterior	Miscellaneous and indeterminate
Number of cases of coronary occlusion	193	48 (25%)	39 (20%)	23 (12%)	59 (31%)	5 (3%)	19 (10%)
Cases showing anomalous pulsation	11	6 (55%)	4 (36%)	0	0	1 (9%)	0
Incidence of pulsatory phenomenon	5·7%	12·5%	10·3%	—	—	20%	—

following groups of cases were recognizable, viz., (1) extensive anterior wall infarcts, 39 cases; (2) extensive anterior wall infarcts with septal involvement, 48 cases; (3) localized anterior wall infarcts, 23 cases; (4) posterior wall infarcts, 59 cases; (5) anterior and posterior wall infarcts, 5 cases; and (6) miscellaneous and indeterminate group of infarcts, 19 cases (Table I). Doubtful cases and those of subendocardial and subepicardial infarction were excluded from this study.

Results

Anomalous præcordial pulsations, during the acute phase of the coronary attack, were observed in 11 (5·7%) of the 193 cases. Of the 11 cases, ten were men and one a woman, ranging in age from 44 to 75 years with an average of 59 years. Four were hypertensive, 1 diabetic, and 3 hypertensive and diabetic; the high incidence of hypertension (64%) and diabetes (36%) was noteworthy. While two of the cases were having their second attack of coronary occlusion, in the remaining nine it was the first attack.

Clinical Characteristics. The anomalous pulsation was located medial to and slightly above the level of the customary apex beat in all 11 cases. In 7, the apex beat was neither visible nor palpable.

On the basis of their relationship to the apex beat, three main types of pulsations were recognized (Fig. 1), viz., (1) Type A (7 cases or 64%) with a single præcordial pulsation, 2 to 6 cm. in

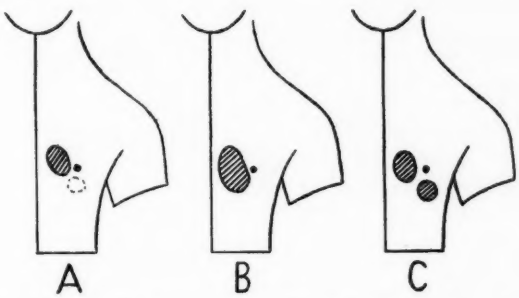

FIG. 1.—Three types of anomalous præcoridal pulsation. A, B, and C.

diameter, rather internal to and above the apex beat which was absent; (2) Type B (3 cases or 27%) with a single wide area of pulsation, 6 to 7 cm. in diameter, caused by the fusion or confluence of the anomalous pulsation with a visible and palpable apex beat; (3) Type C (1 case or 9%) with two distinct areas of pulsation (the so-called " double impulse "), the apex beat and para-apical area of pulsation being separated by a zone of no pulsation.

The anomalous pulsation was observed for the first time during the first week of illness in 7 cases (64%), during the second week in 3 (27%), and during the third in 1 case (9%). With two exceptions (Cases 5 and 11), where the pulsation became permanently established as part of a ventricular aneurysm, it was transitory, lasting for from 4 to 24 days with an average of 13 days.

The following phenomena were observed during the time of the anomalous pulsation, viz., transient auricular fibrillation in one, ectopic beats in two, gallop rhythm in five, and " tic tac " rhythm in three cases. Transitory systolic murmurs over the area of pulsation were noted in two cases.

Electrocardiographic Correlation. On the basis of electrocardiographic localization of myocardial infarcts, the following groups of cases were recognizable (Table I), viz., (1) extensive anterior wall infarcts (4 cases), (2) anteroseptal infarcts (6 cases) and (3) anteroposterior infarcts (1 case). No case belonged to the category of localized anterior wall or posterior wall infarction.

It will be obvious from Table I that the incidence of anomalous præcordial pulsation in acute

coronary occlusion depends greatly on the site of infarction, being more common in cases of extensive anterior wall involvement with or without septal involvement.

Prognosis. Whilst the *immediate* mortality (within 8 weeks of onset of the acute attack) for the coronary group (193 cases), was 15 per cent, it was 27 per cent (3 deaths) for the smaller group of 11 cases with anomalous præcordial pulsations. Paradoxically enough, both cases with second attacks of coronary occlusion recovered, while 3 of the 9 with first attacks proved fatal. Further analyses have failed to establish any relationship between factors like time of onset, duration, extent and type of pulsation, and the immediate outcome of the case.

A Clinical Sign of Value. The clinical sign described here, appears to have some value in diagnosis and prognosis. This diagnostic value was confirmed in two of my cases of chest pain where a diagnosis of myocardial infarction was made, merely on the basis of this sign, several days before cardiographic confirmation. Furthermore, since every case in my series of acute coronary occlusion with this sign was subsequently proved to be one of extensive anterior wall infarction, with or without septal involvement, the localizing value of the sign appears obvious. It appears that in all cases of severe chest pain or of suspected coronary occlusion, the development of an anomalous pulsation over the præcordium is sufficient justification for a presumptive diagnosis of extensive myocardial infarction involving the anterior wall of the heart.

A fatal termination within six weeks of onset of the acute attack was observed in 15 per cent of all cases (193 cases) of coronary occlusion and in 27 per cent of cases showing anomalous præcordial pulsations (11 cases). In view of the higher mortality rate of the latter group, one feels justified in regarding the sign as one of bad prognostic significance. Also, the possibility of aneurysm formation in the near future should be considered as illustrated by Cases 5 and 11 of this series.

Summary and Conclusions

Of a series of 195 cases of acute coronary occlusion where repeated observations and proper follow-up were possible, 11 cases (5·7%) showed at some time or other during the initial four weeks of their illness, a visible and palpable area of pulsation over the præcordium. Located mesial to and above the level of the apex beat, 2·5 to 7 cm. in diameter, the pulsatory phenomenon was transitory in nine and persistent as a parietal or ventricular aneurysm in two of the cases. On the basis of their relationship to the apex beat, three main types of pulsations were recognizable.

Extensive anterior wall myocardial infarction with or without septal involvement was demonstrable in all the cases, electrocardiographically. Evidence is presented to show that the clinical sign described here has some value in the early diagnosis, localization, and prognosis of myocardial infarcts.

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FAMILIAL CARDIOMEGALY

BY

R. T. GAUNT AND M. A. LECUTIER

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Received July 9, 1955

William Evans (1949) described a series of cases of cardiac enlargement in which none of the usual causes of cardiomegaly was present, and among this series of nine cases there were three who were related (a mother and two sons). Moreover, the mode of death in several relatives suggested that a similar condition may have been present in other members of the family. A similar family history had been reported previously in patients with unexplained cardiomegaly on two occasions (Case Records, Massachusetts General Hospital, 1942) and Addarii and Mahaim (1946). A necropsy carried out on one member of the family described by Evans showed an unusual finding in that there were extensive glycogen deposits in the heart muscle; in addition there were areas of dense fibrosis with hypertrophy of remaining fibres. Similar deposits of glycogen were also found in the vastus externus muscle. Glycogen is found in the heart muscle in some cases of Von-Gierke's disease but Evans did not consider his case to be an example of this condition as there was no evidence of a failure of glycogenolysis. Moreover, death has always occurred at an early age in the recorded cases of Von-Gierke's disease that have shown cardiac involvement. Evans concluded that this was a definite syndrome possibly related to Friedreich's ataxia and suggested that it be called familial cardiomegaly.

The purpose of this paper is to present a further series of cases in which there is a familial incidence and in which there are unusual features similar to those described by Evans. One of the cases has been followed to necropsy.

Case Histories

Case 1. A man, aged 49 years, was first seen in August, 1951, when he complained of increasing dyspnœa for the previous three months. Prior to this he had been quite well and had worked in the mines all his life. A month after first noticing shortness of breath, he had two attacks in which he had a transient feeling of faintness and unsteadiness. He ceased working at this time and since then had one further attack. There was no past history of rheumatism.

On clinical examination he had gross cardiac enlargement and a bradycardia (pulse rate 32 a minute). There was no evidence of valvular disease and the blood pressure was 162/90. X-ray examination confirmed the presence of gross cardiac enlargement and a cardiogram (Fig. 1) showed auricular flutter, A-V dissociation, and great increase of amplitude of all complexes. Wasserman and Kahn reactions were negative.

This patient was kept under observation and it was found impossible to affect the rate of his heart by any of the usual measures adopted in heart block. He subsequently developed true Stokes-Adams attacks and although ephedrine in fairly large doses (4 grains daily) seemed to reduce their frequency there was little change in the cardiographic findings.

Case 2. A woman, aged 23 years, came to the Out-Patient Department in November, 1951, complaining of "rheumatism" for three months. Her rheumatism had started in the interphalangeal joints but had subsequently spread to the shoulders and knees and the pains tended to move from joint to joint; she gave a history of occasional sore throats, and slight shortness of breath

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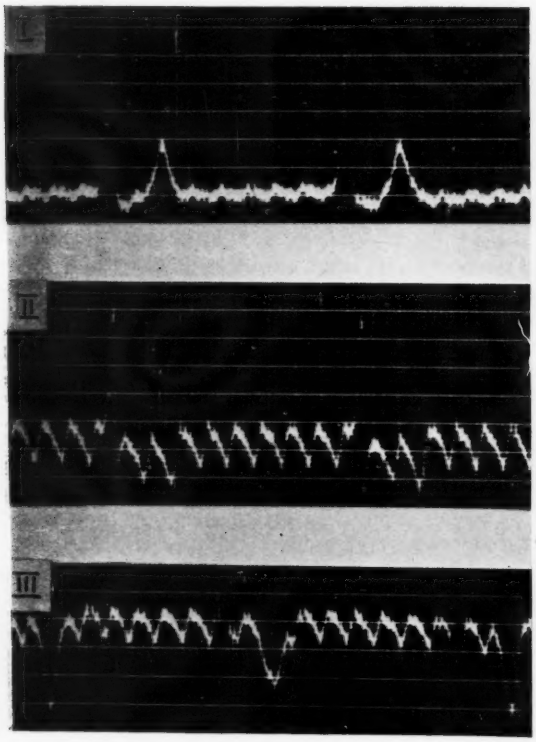

FIG. 1.—Electrocardiogram from Case 1, showing auricular flutter, A-V dissociation, and greatly increased amplitude of all complexes.

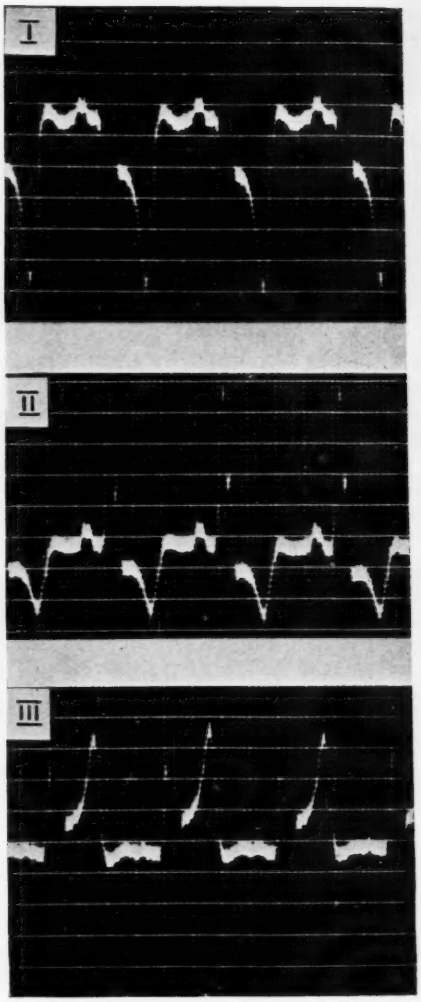

FIG. 2.—Electrocardiogram from Case 2, showing greatly increased amplitude of QRS deflections and T waves, and changes in the S–T segments.

on exertion, but there was no previous history of rheumatism, and she had considered herself quite fit until three months before attending the hospital. On examination there were no obvious joint changes but she was found to have considerable cardiac enlargement and there was also a soft systolic murmur audible both in the mitral and in the pulmonary areas. This was not thought to be of organic significance. Her blood pressure was 138/80. The sedimentation rate was found to be 3 mm. in 1 hour; 7 mm. in 2 hours (Westergren's method). X-ray examination of the chest confirmed the presence of gross cardiomegaly, and the cardiogram (Fig. 2) showed greatly

increased amplitude of the complexes and also gross abnormality of the S–T segments and T waves. A diagnosis of "isolated myocarditis" was made.

Case 3. A woman, aged 53 years, was seen at her home in April, 1952, when she was having frequent and severe Stokes-Adams attacks which had been present for the previous thirty-six hours. There was a history of "collapse" three years previously and she had then been told by her doctor that her heart was affected. Since then she had been short of breath on exertion. She gave a history of chorea at eight or nine years of age. On examination the pulse rate was 6 a minute and the heart was found to be considerably enlarged. The blood pressure was 150/35. She was admitted to hospital and during the course of the next six weeks the pulse gradually returned to a normal rate and the blood pressure rose to 200/100. An electrocardiogram showed complete heart block with complexes of high potential, and the record during recovery is shown in Fig. 3. Wassermann and Kahn reactions were negative.

When Case 3 was first seen at her home, among the relatives present was her daughter who

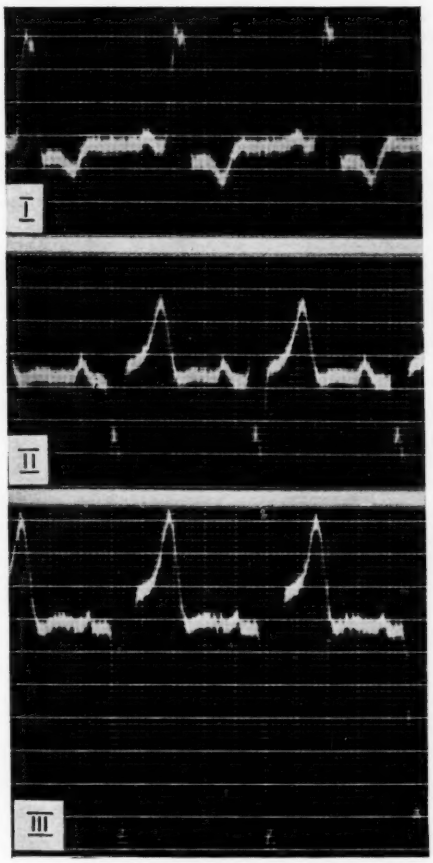

FIG. 3.—Electrocardiogram from Case 3, showing some increase in amplitude of QRS deflections and the T waves of leads II and III and changes in the S–T segments.

was recognized as being the patient described above as Case 2. It was then learnt that Case 1 was also related being the brother of Case 3 (and therefore maternal uncle of Case 2). Several other members of the family were subsequently persuaded to have electrocardiograms taken but none of them would consent to radiological examination. None of the electrocardiograms showed any abnormality.

All three patients had gross cardiomegaly (unfortunately an X-ray examination was not performed on Case 3), and the electrocardiograms showed some form of heart block, greatly increased amplitude of complexes and changes in the S–T segments and T waves suggesting considerable muscular hypertrophy and probable ischæmia. In view of the findings in Evans' series, Case 1 had a biopsy of the vastus externus muscle and this showed heavy glycogen deposits. He died in a Stokes-Adams attack on January 8, 1953, and a post-mortem examination was carried out.

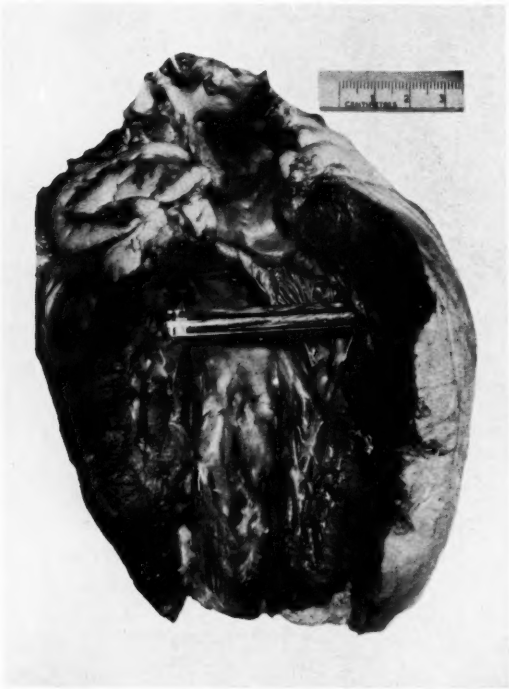

FIG. 4.—Heart of Case 1 weighing 737 g. There is general hypertrophy, especially of the left ventricle.

Case 3 refused further investigation and subsequently died at home; permission for post-mortem examination could not be obtained. Case 2 remained well except for slight dyspnœa on severe exertion; she has since married and left the district.

Necropsy Report on Case 1. Externally, the subject was moderately well nourished and middle-aged; there was no abnormality of note. Internally, the lungs presented a moderate degree of emphysema but otherwise they appeared normal. The heart was much enlarged (Fig. 4) and weighed 737 grams. The walls of all the chambers were hypertrophied, that of the left ventricle being up to 22 mm. in thickness. This measurement is of the wall proper and excludes the papillary muscles, which were also very much hypertrophied. The myocardium presented no

macroscopic abnormality. The valves were normal, as were the septa and the auricular appendages. The coronary arteries presented only a mild degree of atheroma. Nothing else of note was discovered in the heart. The aorta showed a little atheroma. The gall-bladder presented a moderate degree of cholesterolosis and its bile contained a little biliary gravel. All other organs appeared normal macroscopically.

Microscopically, the appearances of the myocardium constitute the main interest of the case. In the sections stained by hæmatoxylin and eosin the most striking feature consists in the presence of multiple vacuoles in the myocardial fibres (Fig. 5). These vacuoles are very prominent in the fibres of the atria, but less so in those of the ventricles. Closer examination reveals well-marked hypertrophy of the individual muscle fibres and this appears to be particularly striking in those fibres showing marked vacuolation.

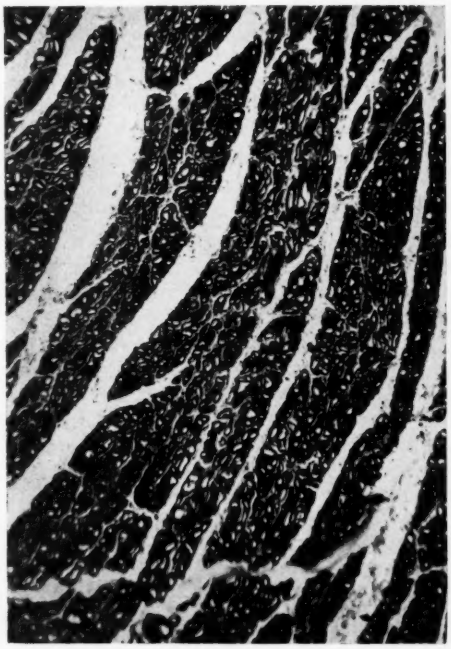

FIG. 5.—Photomicrograph (×80) of myocardium of Case 1, showing marked vacuolation of myocardial fibres. H. and E.

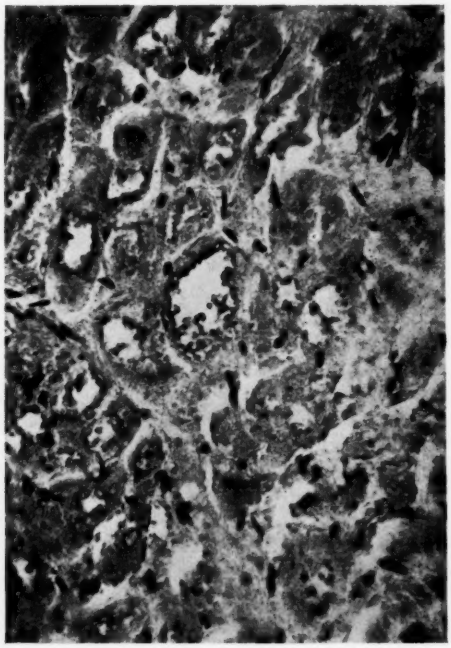

FIG. 6.—Photomicrograph (×360) of myocardium of Case 1, showing deposits of glycogen, particularly in the vacuoles. Best's carmine.

In addition to the hypertrophy and vacuolation of the muscle fibres, there is a moderate degree of patchy fibrosis of the myocardium. In suitably stained sections, traces of fat only were found in the myocardial fibres and none in the vacuoles.

Sections from material fixed in Bouin's solution which preserves glycogen, show conspicuous deposits of this substance in the myocardial fibres (Fig. 6). These glycogen deposits are most plentiful in the vacuoles but they are also evident in other parts of the fibres and in the interstitial tissue. In view of the suggestion put forward by Paulley *et al.* (1954), H. and E. sections and also sections stained by P.A.S. were searched for the parasite of toxoplasma, but without success.

Sections of the spleen, kidney, one adrenal gland, pancreas, thyroid gland and brain were all examined for glycogen deposits with negative results. Glycogen deposits were, however, found in the liver, but not more plentifully than in the liver of a control case. A little glycogen was also found in the tongue. Hæmatoxylin and eosin sections of all the tissues mentioned showed a little congestion or nothing of note.

Control specimens were examined of those tissues that showed the presence of glycogen, viz. the myocardium, the muscle of the thigh and the liver. As already mentioned, the same amount of glycogen was found in the liver of the control case as in the case under discussion. The myocardium and peripheral muscle of the control case, however, showed traces of glycogen only. The occurrence of deposits of glycogen in the normal heart and peripheral muscle has been controlled more fully by Russell (1948) who examined at necropsy eleven cases which showed only scanty deposits of glycogen.

Other Pathological Investigations. A biopsy of the vastus externus muscle taken shortly before death also shows a heavy content of glycogen granules in the muscle fibres. No vacuoles were demonstrated. Glucose tolerance tests were carried out on Cases 2 and 3. These were completely normal with a final normal adrenaline response in each case. The alkali reserve was 54·8 vols. CO_2 in Case 2, and 61·4 vols. CO_2 per 100 ml. in Case 3. The blood cholesterol was 193 mg. in Case 2 and 230 mg. per 100 ml. in Case 3.

Discussion

This series of cases presents features almost identical with those of Evans' (1949) series. Clinically, symptoms have been extremely slight or non-existent until the terminal stages. The first patient worked as a miner without symptoms until two and a half years before his death. The second patient had no cardiac symptoms and continued symptomless until lost trace of. The third patient began having symptoms three years before her death. Both patients who died had Stokes-Adams attacks. All three had gross cardiac enlargement without hypertension or valvular disease.

The electrocardiograms showed a great similarity to each other and also to those of the first two cases described by Evans. The main changes are widening of the QRS deflections, alteration in the S–T segments and T waves and the high potential of the complexes. This finding of high potential which is of the order of 2·5 millivolts, is most striking and would appear to be a particular feature of the familial cases. The high potential is probably related to the marked hypertrophy of muscle fibres and possibly to the high glycogen content. The great mass of muscle would doubtless explain the widening of the QRS deflections.

Pathologically the basic abnormality consists in large deposits of glycogen both in the heart muscle and in peripheral muscle. In the case of the heart, hypertrophy and vacuolation of the fibres, together with fibrosis, are also evident. These changes are entirely absent in a control case. They are essentially the same as those in the main case described by Evans (1949), although in his instance fibrosis appeared to be more prominent while vacuolation and glycogen deposits were less prominent than in the present patient.

All these findings being essentially the same as those described by Evans (1949), the cases here presented support his conclusion that this is a distinct and specific syndrome, for which he proposed the name " familial cardiomegaly."

Davies (1952) described a series of cases with familial cardiac disease. Although there are conduction defects in his cases, the electrocardiograms do not show the gross abnormalities which are present in Evans' series, and also in the present series, namely, great increase in amplitude, widening of the QRS deflections and changes in the S–T segments. Furthermore the appearances at necropsy described by Davies are inadequate. The diagnosis in his series therefore does not appear to be fully substantiated from the electrocardiographic or pathological points of view.

The nature of the condition is somewhat obscure. It is, however, familial and hereditary. There are three conditions with which comparison must be made. The first of these is glycogenic or Von-Gierke's disease, where in a few cases glycogen may be found in the heart, in addition to the liver and kidneys. In Von-Gierke's disease, however, there is a failure in glycogenolysis, as a result of which there is hypoglycæmia, ketosis, and absence of the normal rise in blood sugar after adrenalin, and an abnormal blood sugar curve, this being a little raised and prolonged. These tests were performed on the sister and niece of the patient who came to necropsy, although unfortunately not on the patient himself. All results in both the sister and niece were normal, indicating the absence of any abnormality in glycogenolysis.

The second of the conditions for comparison is Friedreich's ataxia, in which fibrosis and hypretrophy of the surviving fibres is frequently evident in the heart muscle (Evans, 1949; Manning, 1950). No glycogen, however, has so far been discovered in any heart from cases of Friedreich's disease. As fibrosis and hypertrophy of the muscle fibres in the myocardium are in themselves non-specific, it might be considered that there is no real basis for comparison. However, in view of the familial and hereditary nature of both Friedreich's ataxia and the condition under discussion it is possible that they are allied and that future observations will reveal the presence of glycogen in the heart muscle of at least some cases of Friedreich's disease. Roth (1948) quoted by Manning (1950) reports a family in which Friedreich's ataxia affected some members and heart disease (of a familial nature) affected other members.

The third of the similar conditions is progressive muscular dystrophy (myopathy) in which the heart may be involved and show an increase of connective and fatty tissue, with atrophy or hypertrophy of myocardial fibres and also degenerative changes and vacuole formation in these fibres (Storstein and Austarheim, 1955). The authors do not mention whether or not glycogen was present in the vacuoles. The similarity between familial cardiomegaly and progressive muscular dystrophy (also frequently familial or hereditary) when this affects the heart, is thus as noteworthy as that between the former and Friedreich's disease. It would appear therefore that, like Friedreich's disease and the myopathies, familial cardiomegaly is basically a genetically determined condition. It should be clearly understood that in the cases here described there was no clinical suggestion whatsoever that the patients were suffering from any form of myopathy.

Finally, reference must be made to the recent contention by Paulley *et al.* (1954), that familial cardiomegaly *inter alia* is probably a manifestation of myocardial toxoplasmosis. There are several objections to this contention. In the first place no toxoplasmas were found in material from the present case, although searched for in suitably stained sections as indicated above. According to Valentine *et al.* (1953), the parasites are easy to find, being readily visible in H. and E. sections. Secondly, the suggestion is based on inadequate consideration of the histological changes that occur. Thus in the case here described the vacuolation of fibres and the glycogen deposits (not referred to by Paulley *et al.*) must have a close relationship to the ætiology of the condition and there is no information to suggest that similar or related changes have ever occurred in toxoplasmosis. These abnormalities appear to be specific for familial cardiomegaly.

Thirdly, the suggestion of toxoplasmic ætiology can only be correlated with the familial nature of the condition if it is assumed that a special strain of toxoplasma with myocardial affinity is concerned. This is a suggestion put forward by Paulley *et al.*, but it is speculative and is in disagreement with the protean manifestations of all established cases of toxoplasmosis to which Paulley *et al.* refer.

Fourthly, the suggestion is based on serological evidence. While the figures given by Paulley *et al.* for the dye test and complement fixation test in his cases cannot be ignored, they are all low except for the dye test in the third case. The low figures obtained must be balanced against the fact that a low titre of antibodies is found in 28 per cent of the adult population (Valentine *et al.*, 1953). Moreover, recent work has demonstrated the lack of specificity of the dye test in the diagnosis of toxoplasmosis (Awad, 1954).

Summary

Three cases of familial cardiomegaly are described, all in members of one family in whom there was gross cardiac enlargement in the absence of any of the usual causes. All three patients showed a remarkable similarity both clinically and electrocardiographically to those previously described by Evans.

Two of the cases had very little cardiac disability prior to the terminal stages of the disease. The third has suffered very little cardiac disability so far.

In the only necropsy performed large deposits of glycogen were found both in the heart and in peripheral muscle and in addition the heart muscle showed hypertrophy, vacuolation of the fibres, and areas of fibrosis.

The condition is discussed and support is given for the view that the cases presented were suffering from familial cardiomegaly. There is some evidence that this condition is allied to Friedreich's ataxia and progressive muscular dystrophy, both the latter and familial cardiomegaly being genetically determined. There is little to support the suggestion that the condition is due to toxoplasmosis.

Grateful acknowledgment is made to Dr. J. L. Grout for the radiological examinations.

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PAINLESS CARDIAC INFARCTION

BY

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It is tradition to associate coronary arterial disease with pain behind the breast bone. It is also known that pain may be absent when such coronary disease, even in a gross form, has not caused injury to the myocardium. What has not received the same universal recognition is that frank cardiac infarction from coronary occlusion can be present without invoking chest pain.

Gairdner (1891) applied the designation *angina pectoris sine dolore* to patients supposedly without actual pain, but with angor animi and a sense of impending dissolution. Obrastzow and Strascheskow (1910) mentioned that infarction of the heart could take place without causing pain, while Gallavardin in 1921 stated that patients may die of cardiac infarction without ever suffering pain.

In order to facilitate the diagnosis of cardiac infarction when pain is absent, and so apply appropriate treatment early in the illness, there is need to know the circumstances under which it is met. The purpose of this paper is to study this clinical syndrome and to promote a better understanding of it.

The Investigation Outlined

Before patients could qualify for admission into the series that we assembled as examples of painless cardiac infarction, we required that four conditions should be satisfied. First, apart from insisting upon freedom from frank pain in the chest, it was necessary for each patient to deny the presence of like symptoms which included an ache, tightness, a sense of pressure, indigestion, and discomfort. Secondly, the patient had to testify to the absence of these symptoms following direct questioning when the observer's hand was laid on the chest to suggest where the abnormal sensation might have been felt. Thirdly, such close questioning had to take place soon after the start of the illness and at the same time corroboration of the patient's denial of chest pain was sought from a relative, a friend, or attending physician. It became evident early on that any neglect to exercise such care in the selection of patients would have meant the admission of many that were not true examples of painless cardiac infarction. The fourth condition was the finding of an electrocardiogram that showed the marks of cardiac infarction; in patients who died such infarction was sought at necropsy and in each of 11 patients so examined, cardiac infarction was present. Two circumstances contrived to make the electrocardiographic diagnosis difficult. One was the association in so many of left ventricular preponderance from arterial hypertension with a laterally situated infarct; the other was the presence of an arrhythmia which often obscured the changes in the tracing that were the outcome of cardiac infarction.

When such criteria were applied to patients examined in hospital and in private practice during five years, it was possible to assemble 70 examples of painless cardiac infarction, 56 men and 14 women.

Circumstances Favouring the Absence of Pain in Cardiac Infarction

When the symptoms and signs presented by the patients who form this series were examined, there came to light certain circumstances that appeared to decide the absence of pain in cardiac infarction, a condition that characteristically gives rise to a pain often strong enough to cause its host to feel faint unless its sharpness has been subdued by morphine. These circumstances, which are summarized in Table I, will now be considered in turn.

TABLE I

Incidence of Circumstances appearing to determine the Absence of Pain in 70 Patients with Cardiac Infarction

Circumstances which determine painlessness in cardiac infarction	No. of patients	Sex incidence	
		Men	Women
Restricted cardiac infarction	26	19	7
Auricular arrhythmia	21	18	3
Hypertension	9	8	1
Hypertension conjoined with auricular fibrillation	7	6	1
Stokes-Adams disease	? 4	4	—
Vomiting	2	—	2
Cerebral embolism	1	1	—

Auricular Arrhythmia

In this group of patients with painless cardiac infarction all showed auricular fibrillation, flutter, or tachycardia and those with associated hypertension or with heart block were kept apart.

Among the 70 patients, 21 qualified to enter this group, 18 men and 3 women. The average age was 59 years. In 12 the arrhythmia was auricular fibrillation while in 9 it was auricular tachycardia. In 3 patients the abnormal rhythm was of the paroxysmal kind, and in one other, auricular tachycardia changed to fibrillation and this continued as the dominant rhythm. In no patient in this group was syncope a symptom so that the absence of pain appeared to be directly related to the arrhythmia and not to the association of attacks of unconsciousness which seemed to be the cause in 5 of the 15 cases reported by Cookson (1942).

Shortness of breath was present in only 7 of the 21 cases; in 5 of these it was severe at the start of the illness when it assumed the form of cardiac asthma. Likewise, heart failure was present in only 6, and subsequent cardioscopy confirmed the absence of pulmonary congestion in the remaining 15 cases.

Palpitation was both a presenting and lone symptom in 10; when this subsided following therapeutic slowing of the heart rate or a spontaneous return to normal rhythm, cardiac pain was still missing. The arrhythmia, rather than breathlessness, appeared to determine the absence of cardiac pain in patients in this group at the start of the illness although the continued absence of pain caused surprise and is without explanation.

Cardiac enlargement was prominent in one, moderate in 4 and slight or absent in 16, so that its presence seemed in no wise to decide the onset of the abnormal rhythm or the absence of pain.

The clinical progress in 16 was satisfactory following orthodox therapy which included digitalization; it was poor in 5, of whom 2 died.

The site of the infarct, as told from the electrocardiogram, was in the anterior wall of the left ventricle in 13, in the posterior wall in 5, affecting the left branch of the bundle in 2, and the right branch in 1. In 8 of the 11 patients in whom auricular fibrillation had persisted, the electrocardiographic diagnosis of cardiac infarction was straightforward (Fig. 1 and 2). The diagnosis became clearer in 10 cases after they had returned to normal rhythm (Fig. 3 and 4). In 3, one of

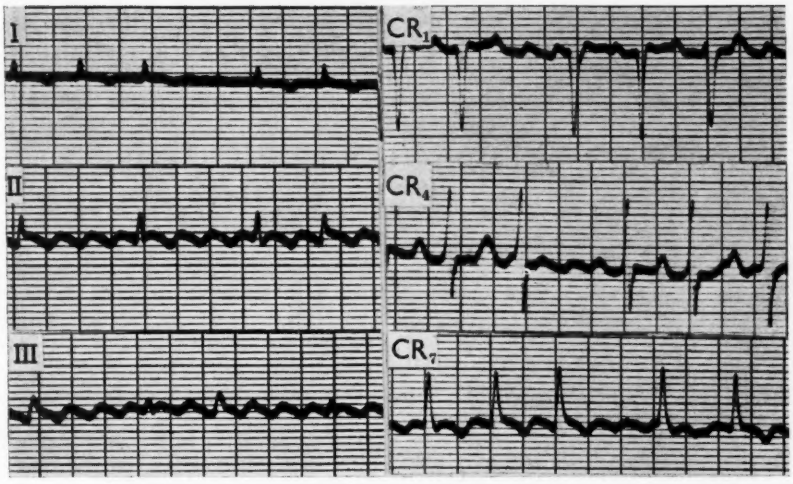

FIG. 1.—*Cardiac infarction and auricular flutter.* The arrhythmia does not conceal the inversion of the T wave in lead I although the same deformity in CR7 is less clear.

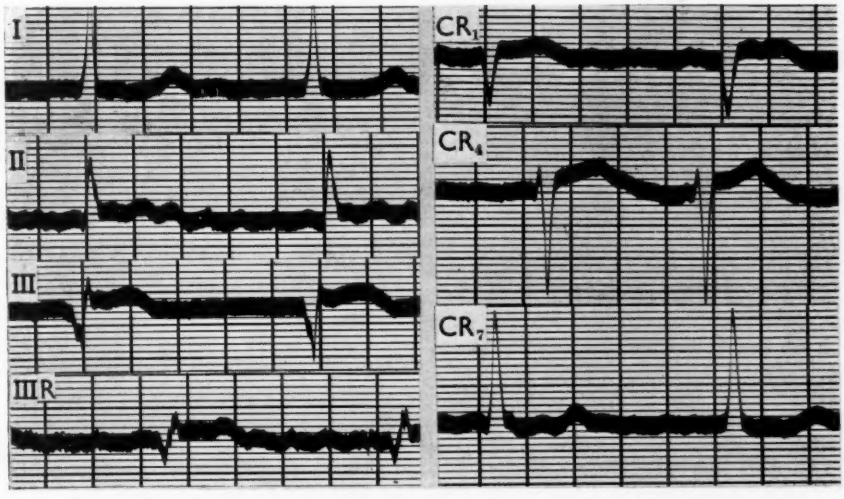

FIG. 2.—*Cardiac infarction and auricular fibrillation.* A Q wave, present in II, is deep and wide in III and IIIR, and the S–T segments are raised in the same leads.

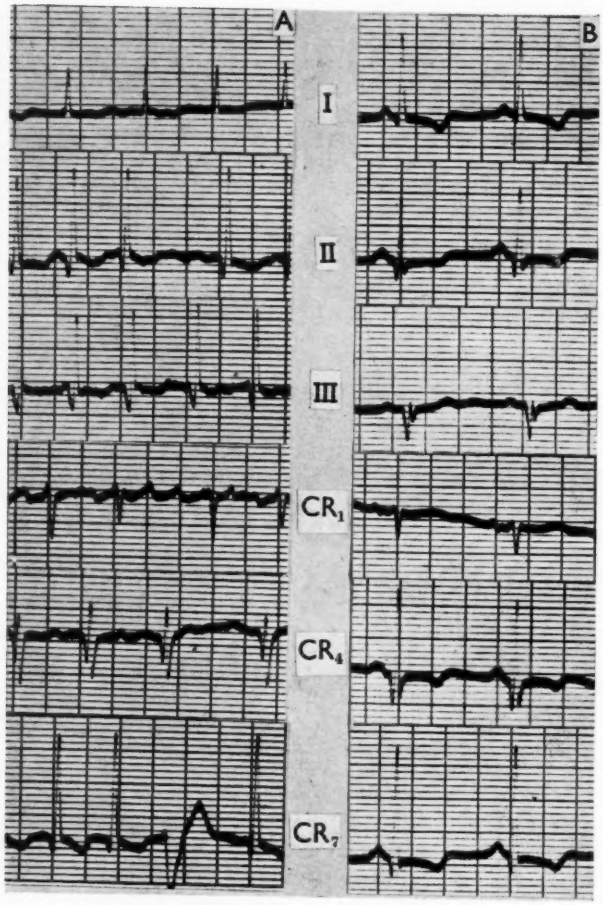

FIG. 3.—*Cardiac infarction and auricular fibrillation.* Fibrillation, present in (A), obscures the signs of infarction, but they are obvious in (B) where normal rhythm has been restored.

them with left bundle-branch block, and each showing the effects of digitalis medication, diagnosis was uncertain for a time.

We have been unable to find any firm opinion expressed on palpitation as a symptom that might prevent the appearance of pain in cardiac infarction. It was a prominent complaint in one of the cases reported by Boyd and Werblow (1937), but they did not allude to it as explaining the absence of pain in their patient.

HYPERTENSION

Arterial hypertension with sinus heart rhythm presented as the obvious form of cardiovascular disease in 9 of the 70 patients with painless cardiac infarction. There were 8 men and 1 woman. The average age was 56 years.

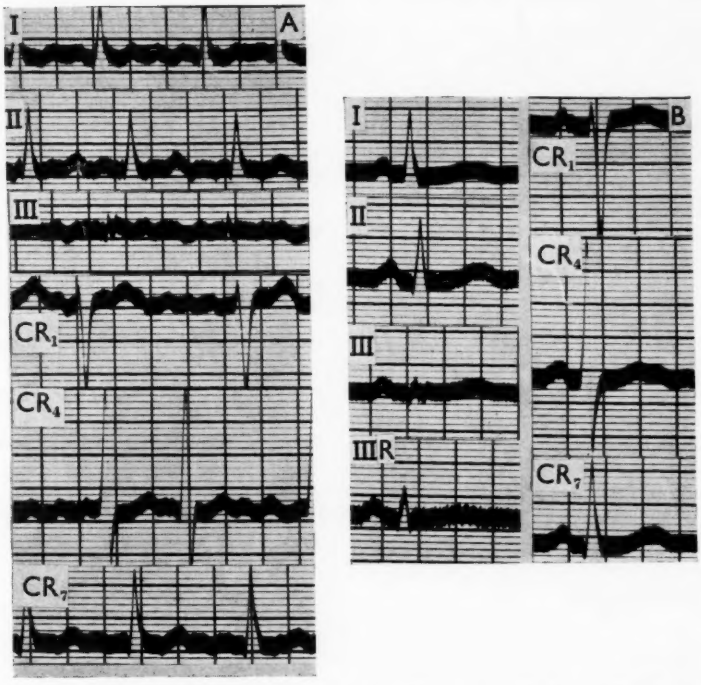

FIG. 4.—*Cardiac infarction and auricular fibrillation.* Fibrillation, present in (A), obscures the signs of infarction, but in (B), showing sinus rhythm, a low and blunt T wave in leads, I, II, CR4 and CR7, confirms the presence of the restricted kind of cardiac infarction.

Breathlessness was present in 7 of the 9 patients, and in 3 it was severe and assumed the form of cardiac asthma. One of these died in the face of orthodox treatment which included digitalization and the use of mercurial diuretics, but progress in the other two was satisfactory. Four patients, who admitted to breathlessness on exertion, remained well, and along with two others without symptoms, had been referred for an opinion on hypertension discovered at a routine clinical examination; cardiac infarction in these cases was an unexpected electrocardiographic finding. One patient had uræmia and this was regarded as contributing to the absence of pain in his case.

Cardiac enlargement, present in each patient in this group, was prominent in 3, while pulmonary congestion was a radiological finding in 4 patients. Triple heart rhythm was an auscultatory sign in 3 patients.

The blood pressure was raised in all, and neither the addition of cardiac infarction nor heart failure had subdued it to a normal level in any. Thus, the diastolic pressure was 110 or over in each of the 9 patients, 120 or over in seven, 130 or over in six and 150 in one.

Allusion has already been made to the difficulty experienced in the electrocardiographic diagnosis of cardiac infarction in the presence of left ventricular preponderance from associated hypertension. In 2 of the 9 patients, left bundle-branch block was not accompanied by additional cardiographic changes, like a Q wave in CR7, which would name cardiac infarction as the cause of the bundle lesion; in one of them, however, cardiac infarction was confirmed at necropsy. In the other 7 patients,

depression of the S–T segment in leads I and CR7 was present in each as an expression of left ventricular preponderance, and evidence of cardiac infarction was considered present if one or more of the following signs had been added to such S–T depression, namely inversion of the T wave in lead I greater than in CR7 (Fig. 5), deformity of the T in CR4 as well as in CR7 (Fig. 6), or

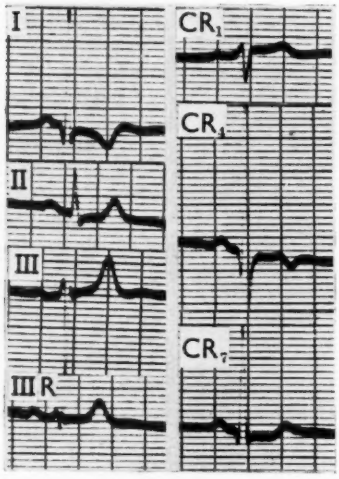

FIG. 5.—*Cardiac infarction and hypertension.* The T wave is inverted in lead I and less in CR4. The S–T is depressed in CR7 and the T in IIIR has lost height.

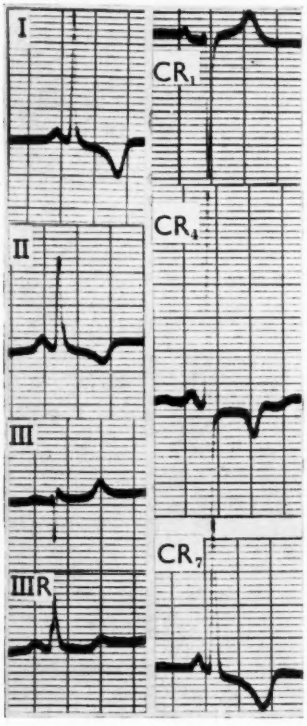

FIG. 6.—*Cardiac infarction and hypertension.* The T wave is inverted in CR4 as well as in I and CR7. The S–T segment is depressed in IIIR but the T wave is also inverted in lead II.

depression of the S–T segment in IIIR in the absence of digitalization and should the T wave in lead II be upright (Fig. 7). In two patients who died and who showed such cardiographic signs, the presence of both hypertension and cardiac infarction was confirmed at necropsy. Less definite signs than these were found in the tracings of some other patients with hypertension, but in the meantime it seemed prudent to exclude these from the series. There is need in the future to cement more securely the cardiographic diagnosis of cardiac infarction in cases that show left ventricular preponderance from hypertension.

Few observations dealing with painless cardiac infarction have directed attention to arterial hypertension as a factor that might contribute to the absence of pain, although Boyd and Werblow (1937) mentioned that a failure to recognize cardiac infarction in the absence of pain had usually happened in elderly subjects with known hypertension. Again, Yater *et al.* (1948), writing on

coronary arterial disease in men aged 18 to 39 years, reported that the blood pressure was raised in 19 of the 23 examples who had not complained of pain.

Parkinson and Bedford (1928) were among the first to draw attention to the fact that dyspnœa might displace pain from the clinical picture of cardiac infarction. The effect of dyspnœa in subduing such pain has since been mentioned by others including Papp (1952) and Roseman (1954). When emphasizing the overshadowing of pain in cardiac infarction by paroxysms of cardiac asthma, most writers have spoken of the entry of such dyspnœa from heart failure complicating coronary arterial disease, and not as the outcome of hypertensive heart failure. Bedford (1939), commenting on the absence of pain in patients where dyspnœa overshadowed it, said that it was specially common in patients who already suffered from heart symptoms or even some degree of heart failure, and that cardiac asthma in a patient with a normal or low blood pressure and without aortic valve disease, suggested coronary occlusion. Similarly, Friedberg (1950) stated that the onset of sudden pulmonary œdema and intensification of heart failure pointed to cardiac infarction without pain. Gilchrist (1951) also mentioned that cardiac asthma in an elderly patient usually meant coronary disease.

Conjoined Auricular Arrhythmia and Hypertension

Since both auricular arrhythmia and hypertension were found separately as circumstances that favoured the absence of pain in cardiac infarction, it caused no surprise to find both conditions present side by side in some of the patients within this series. There were 7 such examples, 6 men and 1 woman. The nature of the arrhythmia was auricular fibrillation in every case.

Breathlessness, present in 6 patients, was severe in 5 at the onset of the illness when it assumed the form of cardiac asthma. Palpitation was the uppermost symptom in only one patient.

There was either moderate or greater cardiac enlargement in every case, and similarly pulmonary congestion was seen at cardioscopy in each. Triple heart rhythm was present in only three as treatment was under way in each patient before we examined them.

In spite of the presence of cardiac infarction, and of heart failure in most of the cases, the diastolic blood pressure was 110 or over in 7, 115 or over in 6, 120 or over in 5, 130 or over in 3, and 150 in one.

Hypertension with or without heart failure appeared to account for the absence of pain in most patients within this group, and only in one was arrhythmia considered to be responsible.

Progress in every patient has been unsatisfactory in the face of adequate treatment. Five of the patients have died and the remaining two are precariously ill.

The electrocardiographic diagnosis of cardiac infarction in patients in this group was frustrated by the persistence of auricular fibrillation in 3, by left ventricular preponderance, and by digitalization which had been started in most of them before the diagnosis of infarction was considered and while heart failure alone was thought to be operating. The electrocardiographic diagnosis was possible in 5, and although it remained doubtful and presumptive in the other two, the presence of cardiac infarction was confirmed at necropsy in both cases.

Restricted Cardiac Infarction

The electrocardiographic changes that follow *salient* or extensive cardiac infarction are plain to see, but when the myocardial injury is *restricted* or limited in its distribution the changes are less obvious and in many instances they escape detection if they are not deliberately sought (Evans and McRae, 1952). The pain associated with such lesser changes is not always correspondingly less severe except that it is never accompanied by shock or heart failure, and only occasionally by arrhythmia, triple heart rhythm, or slight cardiac enlargement. It was expected, therefore, that instances of restricted infarction would appear in our series of painless infarction.

There were 26 such patients, 19 men and 7 women. The average age was 55 years. The myocardial injury was discovered fortuitously for none came with serious symptoms nor showed any abnormal signs except for triple rhythm in 3. They attended for a medical examination which

happened to include an electrocardiogram. The deliberate omission of any intentional search for electrocardiographic abnormalities in patients without chest pain, and in whom for that reason cardiac infarction is not suspected, accounts for the relatively small proportion of such cases in our series. It is likely that routine electrocardiography in uncomplaining elderly subjects over the age of 60, would increase substantially the number of patients in this group. In our opinion, however, any deliberate search for such cases would be unwise unless intended as a limited inquiry carried out as part of a research project.

The diagnosis of restricted infarction in our cases rested on the following cardiographic findings: depression of the S–T segment in 15, a low T wave in leads I and CR7 in 5, a bifid T wave in CR4 in one, and the appearance of a Q wave in lead IIIR, which had been absent in III, in 5 patients. If the significance of any of these changes remained in doubt the tracing was repeated after strenuous exercise when the validity of the cardiographic sign was confirmed.

The progress in all 26 patients had been satisfactory when they were first examined. Subsequently, one patient experienced extension of his cardiac infarction, with the exhibition of typical cardiac pain. Another died of typhoid when abroad and there was no necropsy. A third died of a cerebral accident and at necropsy extensive coronary atheroma was associated with slight changes in the myocardium. A fourth presented minor functional symptoms at his first visit when a routine electrocardiogram showed restricted cardiac infarction; two years later he was re-examined a fortnight after experiencing a sense of tightness in the chest and on that occasion the electrocardiogram showed the signs of salient infarction providing evidence of extension of the original infarct.

Sutton and Lueth (1930) and Sutton (1931), from their experiments in the dog and from their experience with coronary arterial disease in man, stated that the pathway of pain, arising from faulty nutrition of the heart muscle, was by way of the nerve fibres that lie in the adventitia of the coronary arteries. They stated that the absence of pain which may be met with, even in the presence of extensive coronary disease, was due to an efficient anastomosis between branches of the coronary arteries, and that the severity of the pain varied with the degree of closure of the artery and with its size. Again, Sutton and Brandes (1931) opined that myocardial function, and similarly the presence of cardiac pain in coronary atherosclerosis, depended upon blood flow and not on scarring, and varied with the efficiency of the anastomosis. We agree with their conclusions and emphasize that in patients with restricted cardiac infarction it is the tardy progress of the infarction that explains the absence of pain and not the smallness of the infarct, for in a separate series of 328 patients with restricted infarction collected by Evans (1956) there was cardiac pain which was indistinguishable from the pain associated with salient cardiac infarction that showed obvious cardiographic changes.

One patient, a man, aged 53 years, who had been accepted for the series was later excluded; although without any complaints he had applied for a routine medical examination following the unexpected death of a friend. The finding of a bifid T wave caused surprise and was accepted as evidence of a myocardial injury from coronary arterial disease which had formed in the absence of pain. Extension of the deformity in an exercise electrocardiogram (Fig. 8) appeared to confirm this view. He reported for re-examination a year later and was still symptom free. A normal electrocardiogram on this occasion gave rise to suspicion as to the validity of the initial diagnosis of painless cardiac infarction, and some other cause of the cardiographic deformity was sought. The alternate explanation of the blemish in the first tracing came with the patient's confession, which followed direct questioning, that for many years prior to his first examination his daily consumption of whisky had exceeded 20 ounces (570 ml.). It is likely, therefore, that alcoholic myocarditis had caused the initial changes in the electrocardiogram which had resolved when the patient had assumed more temperate habits. This example points the lesson that when lesser electrocardiographic changes recover wholly a temporary myocardial injury has caused them, and equally that if such changes persist and spread, restricted cardiac infarction from coronary arterial disease is the cause even in the absence of cardiac pain when the process has been a gradual one.

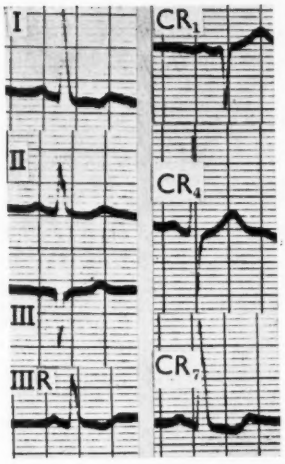

FIG. 7.—*Cardiac infarction and hypertension.* There is greater depression of the S–T segment in CR7 than in I. The T wave is upright in lead II and the S–T is depressed in IIIR.

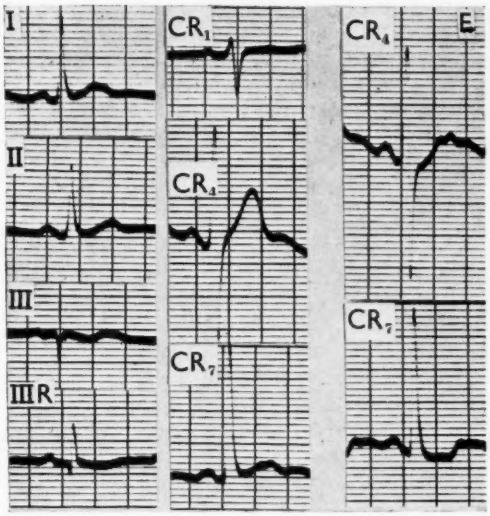

FIG. 8.—*Alcoholic myocarditis.* In the resting electrocardiogram the T wave is blunt in leads I and CR7; the exercise tracing (E) is regarded as abnormal.

OTHER CIRCUMSTANCES

When the absence of pain in cardiac infarction had been attributed either to auricular arrhythmia or hypertension in 37 patients and had been found as a feature of 26 patients with restricted cardiac infarction, there remained 7 in whom some other contingency appeared to be responsible for such painlessness. The circumstances that might have contributed to the absence of pain in these patients will now be separately examined.

Stokes-Adams Disease. Although 4 patients are considered under this head, if the definition of the syndrome is strictly adhered to as a clinical state where unconsciousness is associated with heart block, it is doubtful whether any were true examples of it.

The illness in two patients was heralded by a syncopal attack, and both denied chest pain after recovering consciousness. Neither patient was in a state of collapse when emerging from the attack. The electrocardiogram, which exhibited obvious changes from cardiac infarction, showed no kind of heart block. Subsequently, when both patients were re-examined, no further syncopal attacks had taken place, the cardiogram continued to show sinus rhythm and the same frank inversion of T waves, while cardiac pain was still absent. If these two patients are to be regarded as examples of Stokes-Adams disease, the heart block must have been of the transient variety.

The third patient in whom the electrocardiogram confirmed the presence of complete heart block and unequivocal changes of cardiac infarction, had never experienced unconsciousness. There was only moderate enlargement of the heart when viewed by cardioscopy, and there was no pulmonary congestion.

The fourth patient was examined because of recent giddiness which visited him unawares causing him to sway and lose his balance, but he denied ever being unconscious. No abnormal physical signs were uncovered during clinical examination, and it caused surprise to find characteristic electrocardiographic changes of cardiac infarction with sinus rhythm. Here again, there may

have been transient heart block during the attacks of severe vertigo, but proof of this was not obtained, and his progress has been satisfactory since the paroxysms ceased.

Fainting or collapse had taken place in 4 out of 17 patients with painless cardiac infarction reported by Pollard and Harvell (1940), while Cookson (1942) observed a syncopal or epileptiform episode in 15 patients with recent cardiac infarction in whom pain was either slight or absent. Friedberg (1950) also mentioned dizziness as the chief symptom in many patients in whom pain was absent.

Vomiting. Although vomiting was a noticeable symptom in four patients, two have been included in other groups, for in one arrhythmia rather than vomiting was considered responsible for the absence of cardiac pain, while in the other patient with complete heart block vomiting might have been a factor contributing to keep the pain at bay.

In two cases, however, severe vomiting was the only presenting symptom. One patient, a woman, aged 62 years, was taken ill with unexpected vomiting while attending a cinema. She vomited twice before she could leave the building; there was no pain and she walked home where severe vomiting recurred. That evening she felt very ill and fainted four times. Thereafter, she improved, but two months later she experienced undue breathlessness on walking. When examined there was triple heart rhythm, moderate generalized cardiac enlargement, and pulmonary congestion, and obvious electrocardiographic signs of cardiac infarction. She responded well to treatment with rest, digitalization, and four injections of a mercurial diuretic. The second patient was a woman, aged 78 years, who was taken ill with sudden and severe vomiting; when her medical attendant arrived the vomiting had ceased, but as her pulse was rather small and she seemed frail, he gave instructions that he should be recalled if her condition deteriorated. A few hours later, vomiting again set in, and she died soon after. She had denied emphatically that there was any pain in the chest or elsewhere. At necropsy recent cardiac infarction was found to have resulted from coronary thrombosis complicating coronary atheroma.

Although sudden nausea and vomiting has seldom been named as a symptom that might obscure pain in cardiac infarction, Pollard and Harvell (1940) found it in 5 among their 17 cases of painless infarction.

Cerebral Embolism. Dozzi (1937) wrote about cerebral embolism or thrombosis as another circumstance that might obscure a history of pain in cardiac infarction. He pointed out that in this event the diagnosis was directed to the cerebral vascular accident, and the primary cardiac lesion was overlooked. Thus, in 1000 consecutive cadavers he found 12 instances of cerebral thrombosis or embolism among 41 cases of cardiac infarction, and in only two had the heart condition been recognized. This frequent association of the two lesions suggested that in all cases of cerebral infarction, the possibility of cardiac infarction and intracardiac thrombosis as the source of the embolism, should be kept in mind. Levine (1945) also emphasized the importance of this association, stating that when a sudden hemiplegia takes place in a patient whose blood pressure is not remarkably raised, the diagnosis of cerebral hæmorrhage is too often made, for in some of these cases, unsuspected cardiac infarction may be the source of the embolism.

The fact that only one such example of painless cardiac infarction appears in our series is not meant to emphasize the rarity of this association because our patients were assembled on account of symptoms that more often pointed to a fault in the heart rather than the brain; moreover they form a clinical group rather than necropsy material. Our patient was a man, aged 54 years, who developed a right hemiplegia overnight. He woke up at the usual time and became alarmed when he found that his right arm and leg were paralysed and his speech affected; he had not experienced any pain in the chest nor did it develop during convalescence. He was referred for examination of the heart because of the absence of hypertension and other known causes of a cerebral accident, and the electrocardiogram showed characteristic changes of cardiac infarction.

The Unreliable Witness. We anticipated that amnesia following heavy narcosis, induced by morphine at the start of the illness, might be responsible for the absence of cardiac pain in a number

of patients. Indeed, such instances came to our notice, but since one of the conditions for acceptance into the series stipulated that a friend or attending physician, who might have witnessed the start of the illness, had also to testify to the absence of pain, these were rejected as examples of painless cardiac infarction. One patient, included in the hypertension group, suffered from uræmia, and this might have dulled his appreciation of pain in the chest, if it had been there.

There was, however, one outstanding example of the wilful witness who deliberately suppressed a history of cardiac pain in order to gain profit from a medical certificate testifying to his satisfactory state of health. He was a man, aged 56 years, who had been referred for special examination connected with his application for admission to a superannuation scheme. His acceptance for the scheme depended on a medical report which would endorce his fitness for work, and his likelihood to continue his duties as a servant of a Borough Council until he reached the age of 65 years. Under these circumstances the patient found it to his advantage to hide his symptoms so that even on direct questioning he denied ever experiencing chest pain. The electrocardiogram, however, testified to the undoubted presence of cardiac infarction (Fig. 9). Later, when his admission to a superannuation scheme had been rejected he confessed to experiencing typical cardiac pain.

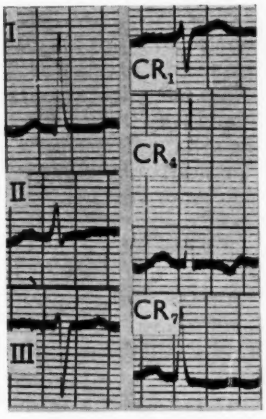

FIG. 9.—*Cardiac infarction.* The T wave is flat in leads I and CR7, and is inverted in CR4.

THE INCIDENCE OF PAINLESS CARDIAC INFARCTION

Considerable discrepancy is found among the figures given by the several authors who have written on the frequency with which pain is absent in patients with cardiac infarction. Many have suggested that the syndrome is a common one. Thus, Davis (1932) found 38 per cent without pain among 76 patients, Saphir *et al.* (1935) 38 per cent among 34 cases, Boyd and Werblow (1937) 33 per cent among 127 cases, Bean (1938) 28 per cent among 300 cases, and Gorham and Martin (1938) 40 per cent among 100 cases. Other authors have met with the condition less often. Thus, Master *et al.* (1937) found only 8 examples of painless cardiac infarction among 530 patients, Babey (1939) one among 116 cases, Pollard and Harvell (1940) 32 among 375 cases, Warner (1951) none among 200 cases, Roseman (1954) 10 among 220 cases, and Gerther *et al.* (1954) 4 among 200 young adults.

Four circumstances materially affect figures denoting the incidence of painless cardiac infarction. First, if pain is so defined as to exclude such sensations described by patients as *discomfort*, *tightness*, *pressure*, and *indigestion*, the incidence of this syndrome will be inevitably high. Secondly, if the

data are collected from case records not compiled under the personal supervision of the author, a statement on the absence of pain is likely to be unreliable and its incidence too high. Even a denial of any pain should be met with direct questioning about the presence of discomfort while the observer's hand rests inquiringly on the patient's chest; if a confession of pain is still not forthcoming a final appeal should be directed to a relative or doctor who might have witnessed the initial attack. Thirdly, little credence should be given to the evidence of a patient taken sometime after the event, or when the shock of a salient cardiac infarction is not long passed, or while recovering from the effects of a major operation or recent narcosis; a patient can be too ill to complain of pain. Fourthly, as our knowledge of the electrocardiographic signs of restricted cardiac infarction increases, and the practice of recording cardiograms in uncomplaining elderly subjects becomes commonplace, so will instances of painless cardiac infarction multiply in number.

For these reasons we do not intend to give the incidence of the condition as it appeared in our series, but instead we wish to emphasize the circumstances that favour the absence of pain in cardiac infarction, so that our increased awareness of the likely presence of this contingency should lead to its readier recognition and to the immediate treatment appropriate to it.

The Cause of Painlessness in Cardiac Infarction

Even when the circumstances associated with painless cardiac infarction are known, the precise way in which these work to exclude pain is not understood. Libman (1926) and Carr (1935) considered that patients with painless cardiac infarction were insensitive to pain, and Libman devised a test intended to establish this hyposensitivity in the individual, where the painful response was estimated when the thumb pressed the great auricular nerve against the styloid process. Herrick (1929) opined that certain areas of the heart were silent or less sensitive than others, or that a gradual narrowing of an artery slowly destroyed vessels, nerves and functioning muscles, causing anæsthesia in the part, so that the final complete obstruction happened less suddenly and in prepared ground.

Wearn (1923) and Hamman (1934) stated that when cardiac infarction supervened in a patient with pre-existing signs and symptoms of heart failure, pain may be absent, and Hay (1933) considered that pain was likely to be absent in the second or third attack of infarction. Bruenn and others (1936) on the other hand believed that those patients with no symptoms prior to the acute episode were most likely to experience painless cardiac infarction.

We found that in the group of patients in whom auricular arrhythmia appeared to have determined the absence of pain, the heart had usually remained unaffected until the onset of the illness. Thus, among the 21 patients, cardioscopy could not find any significant cardiac enlargement in 16, nor pulmonary congestion as an early sign of heart failure in 15. Indeed, in this group the painlessness of the infarct was independent of the presence of previous heart disease and was the direct result of the arrhythmia. Moreover, it was never apparent that the symptom of palpitation had overshadowed the symptom of pain, but rather had it eclipsed or prevented its very inception.

The combined groups of patients with hypertension and hypertension conjoined with auricular arrhythmia, provided 16 examples of painless cardiac infarction, and in these we examined the mechanism whereby pain was absent, with reference to the influence that might be exerted by cardiac enlargement or by breathlessness and heart failure. Enlargement of the left ventricle with left ventricular preponderance in the electrocardiogram was present in each of the 16 cases and in 6 there was great enlargement. Breathlessness was absent in 3 while in 8 of the remaining 13 cases it took the form of cardiac asthma for a time, but even when this symptom abated following treatment and the patient became ambulatory, cardiac pain remained absent. Pulmonary congestion, elicited at cardioscopy, was present in 11 and absent in the other 5. Here, too, it became clear that the limitation of activity imposed on a patient did not explain the absence of pain because it continued to be absent when effective treatment had enabled the patient to return to greater physical activities. The presence of heart failure, therefore, in no wise determined the absence of pain in cardiac infarction. It was evident, too, that breathlessness did not overshadow the pain, unless in

such cases as were too ill for a time to make their complaints known, where it will remain difficult to pronounce on the precise circumstances that are operating. The absence of pain in this group appears to be related to the increased muscle mass which is present in hypertension and which may determine a slower rate of muscle necrosis resulting from infarction which follows coronary occlusion.

In the largest group of patients without pain, namely those with restricted cardiac infarction, we believe that the absence of pain is directly related to the tardy closure of the atherosclerotic coronary branches, a view put forward first by Sutton (Sutton and Lueth, 1930; Sutton, 1931) and later by Mullen (1934). Keefer and Resnik (1928) also thought that in patients with slow infarction the painful impulse might not be sufficiently intense to reach the sensorium.

Summary and Conclusions

Among patients with cardiac infarction examined in private and hospital practice during the past five years there were 70, 56 men and 14 women, in whom pain was absent.

An ache, discomfort, a feeling of pressure or tightness or indigestion, sensations that a patient might regard as akin to pain, were accepted by us to mean pain, and they, too, were absent in the 70 cases that we describe. Moreover, we required each patient to deny the presence of such symptoms following direct questioning while the observer's hand rested on the chest suggesting the place of the discomfort. Further, should the illness have started unexpectedly we sought confirmation of the absence of pain from a relative, friend, or attending physician, who might have witnessed its onset. There was one patient who wilfully denied the experience of chest pain on effort, in an attempt to gain profit from a favourable medical report. Lastly, the electrocardiogram had to show indisputable evidence of cardiac infarction.

Foremost among the conditions that appeared to determine the absence of pain, and featuring in 21 cases, was *auricular arrhythmia*, usually in the form of auricular fibrillation and sometimes auricular tachycardia. Such arrhythmia occasionally frustrated the electrocardiographic diagnosis of cardiac infarction, but when sinus rhythm was spontaneously restored, as happened in one-half of the cases, the graphic interpretation became easier; even then the patient, during increased physical activities, remained free from chest pain.

Hypertension, with normal sinus rhythm in 9 and auricular fibrillation in 7, also proved a deterrent to pain in cardiac infarction. Although many of these suffered from paroxysms of cardiac asthma, we do not attribute the absence of pain to any overshadowing of the symptom by breathlessness, but consider that a tardiness of the process of infarction in a heart muscle enlarged in the course of hypertension was mainly instrumental in preventing the advent of pain.

In 26 patients the absence of pain was associated with *restricted infarction* which had been discovered fortuitously at an examination that happened to include electrocardiography. This number would have increased manyfold if a cardiogram had been recorded deliberately in uncomplaining subjects over the age of 60 years. It is known that patients with this limited kind of infarction commonly suffer characteristic cardiac pain, and we believe that the absence of pain is determined not by the smallness of the infarct, but by the slowness of infarction, which in turn depends on the rate of arterial closure, the limitation of coronary blood flow, and the efficiency of the collateral circulation.

Other circumstances proving inimical to pain in cardiac infarction appeared less frequently; these included *Stokes-Adams disease* which may have played a part in 4 patients, severe *vomiting* which supplanted pain in 2 cases, and *cerebral embolism* which appeared to have subdued pain in one patient.

In the uncovering of disease, to know is to seek, and to seek is to find. To know the circumstances that favour painlessness in cardiac infarction is to seek the condition in elderly subjects with auricular arrhythmia of uncertain origin, or with hypertension. To find it present in any patient affects the outlook, and invites appropriate treatment early in the illness.

We are indebted to Dr. D. M. Blend for placing at our disposal the careful notes he had compiled in the case of his patient in whom severe vomiting was the only symptom of cardiac infarction which caused her death within a short time of the start of her illness.

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CASE REPORTS

PULMONARY HYPERTENSION IN DERMATOMYOSITIS

BY

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Dermatomyositis is the term used to designate a group of cases characterized predominantly by non-suppurative inflammation and degeneration of muscle, including the myocardium, together with similar involvement of overlying or unrelated parts of the skin and hypoderm. Clinical features include fever, erythematous skin lesions, and muscle fatiguability, weakness, pain, and tenderness, which may progress to atrophy and fibrotic contractures. Œdema, particularly over affected muscles and in the orbits, a toxic alopecia, and high levels of creatinuria also commonly occur.

Publications on dermatomyositis have failed to exclude two other confusingly similar conditions: (*a*) the polymyositic form of polyarteritis nodosa, an acute fulminating or self-limiting condition responding well to cortisone or A.C.T.H., in which cutaneous pleomorphism, œdema, muscle tenderness and leucocyte counts are all excessive, and (*b*) an acute " dermatomyositis " which is symptomatic of concurrent carcinoma or lymphoblastoma and is potentially reversible with successful treatment of the neoplasia. True dermatomyositis has an insidious—rarely subacute—onset and runs a slow inexorable course with remissions and relapses towards crippling and grotesque contractural deformities with late poikiloderma, diffuse calcinosis, and the Raynaud phenomenon with sclerodactyly. Moreover, it is a systemic disease and through degenerative and proliferative changes in the connective tissue and in the arteriolar walls, cases may occur of primary involvement of serous membranes, the joints, the alimentary tract, the spleen, the liver, and the lymph glands.

Though there are eminent authorities like Dowling (1952) who maintain that dermatomyositis and diffuse systemic sclerosis are one and the same disease, there is a weight of opinion that there are essential differences in the ætiology, clinical picture, and courses of these conditions. Scleroderma, which should be regarded as a symptom and discarded as a synonym, has recently been admirably reviewed by Cullinan and Harper (1953).

Case Report

I.G., aged 34, a railway signalman, was first admitted to hospital in February, 1949. Prior to the summer of 1948 he had been in excellent health and capable of strenuous activity. In October, 1948, after a month or so of vague malaise and lassitude he developed a bright red rash on his brow and cheeks, with transient orbital swelling. By Christmas, 1948, when the rash had all but faded, pain and tenderness developed in the region of the joints of his fingers, wrists, elbows, and knees. Before admission, he became fevered, and severe pain and later weakness successively affected the muscles of his shoulder girdle, arms, buttocks, legs and, finally, the dorso-lumbar region, so that he became quite helpless. At this time an X-ray of the chest showed no abnormality of heart or lungs—cardio-thoracic ratio 0·4 (Fig. 1). A generalized alopecia followed and he began to have intermittent attacks of the Raynaud phenomenon in his fingers. Remissions and relapses of his joint and muscle symptoms followed and when admitted again to hospital in January, 1951, he was found to be grossly emaciated (weight 76 lb. as compared with 150 lb. in 1948) with generalized muscle atrophy and fibrotic contractural deformities of elbows and wrists and rheumatoid appearances of his hands, with radial or ulnar deviation at the metacarpo-phalangeal joints and flexion at the proximal and hyperextension at the distal interphalangeal joints. Slight poikiloderma of the skin of his brow and sternal area was present. Investigations then showed: E.S.R., 95 mm./hour; plasma proteins total, 6 g. per 100 ml, (albumen 2·8, globulin 3·2, ratio 0·87/1); urinary creatine, 350 mg./24 hours; 17 ketosteroids, 5 mg./24 hours; skin biopsy, " collagen degeneration " with scanty perivascular round cell reaction in the corium; muscle biopsy, focal degenerative changes of variable severity, no notable vascular lesion other than scattered lymphorrhages; X-ray, slight cardiac enlargement with prominence of the pulmonary artery and of its main branches, cardiothoracic ratio 0·5; electrocardiogram, marked right ventricular

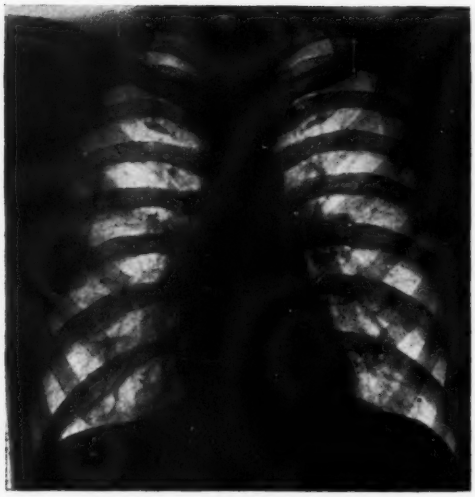

FIG. 1.—X-ray of chest in June, 1949, showing no abnormality of the heart or lungs.

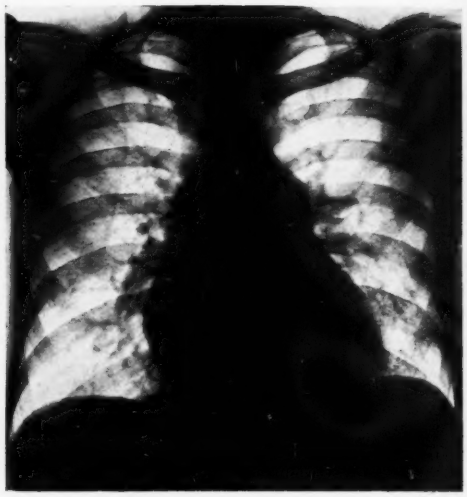

FIG. 2.—X-ray of chest in June, 1954, showing enlargement of the heart and marked prominence of the pulmonary trunk and its main branches. The peripheral vascular shadows, particularly in the upper lobes, are less evident than usual.

hypertrophy. Short courses of A.C.T.H. were given during early 1951 without any objective improvement. Later in that year his illness was marked by two episodes of acute pericarditis and by the development of generalized subcutaneous calcinosis with osteoporosis and the extrusion of chalky bodies from indolent ulcers over bony prominences. At Christmas, 1951, vigorous neck vein pulsation was first noted. Late in 1952 he had recurrent ascites without ankle œdema and a right pleural effusion, but he slowly became ambulant and left hospital in June, 1953. His physical activities were considerably restricted by his locomotor disabilities which made it difficult for him to appreciate his undoubted cardiac and respiratory insufficiency. He returned for review in May, 1954, and from the muscular and cutaneous aspect appeared to have reached a stage of stability. Faint erythema and thickening of the skin of his brow, sternal area, and the extensor surface of his forearms were present without binding to underlying structures. Generalized fibrous muscle atrophy was evident affecting noticeably the facial muscles and masseters to give a cadaveric facies, and the chest muscles to limit much expansion. His fingers were long, thin, and blue, and still showed rheumatoid deformities. Nodules of calcium were palpable subcutaneously in many places, particularly about the tendons. His cardiac and respiratory systems were investigated in detail at this time.

Respiratory System. Expansion of the chest was severely restricted. There were scattered rales at both lung bases and a pleural rub in the right axilla. Tests of respiratory function were done by Dr. C. D. Needham.

Lung Volumes	*Observed*	*Predicted*
Vital capacity	2650 ml.	4200 ml.
Inspiratory capacity	1290 ml.	2700 ml.
Expiratory capacity	1360 ml.	1500 ml.
Resting tidal air	650 ml.	—
Residual volume	2270 ml.	2200 ml.
Total lung capacity	4920 ml.	6200 ml.
Helium mixing	98%	>60%
Functional residual capacity	3630 ml.	3350 ml.

Ventilatory Measurements. (*a*) Timed vital capacity at 2 sec. was 2550 ml., i.e. 96 per cent of total vital capacity (normal greater than 95 per cent). (*b*) Maximum breathing capacity was 84 litres a minute (normal average is 124 litres a minute).

There was, therefore, a great diminution in inspiratory capacity but emphysema was excluded because (1) maximum breathing capacity was only moderately diminished, (2) there was no air trapping as shown by (*a*) above, (3) intrapulmonary mixing was above average, and (4) functional residual capacity was normal.

X-ray screening of the chest showed that the right ventricle was enlarged and the pulmonary artery segment prominent. Pulsation of the heart seemed normal. There was no sign of calcification of the pericardium and no evidence of enlargement of the left atrium. Cardio-thoracic ratio was 56 per cent (Fig. 2). Tomograms confirmed the enlargement of the main pulmonary artery and its primary branches. The peripheral vascular shadows in both upper zones were less than normal. No other abnormality was seen in the lungs.

Cardiovascular System. There was no cyanosis or œdema. Marked venous pulsation was seen 2 cm. above the sternal angle as the patient reclined at 45°. Two waves could be distinguished: a jugular venous pulse tracing, with simultaneous electro- and phono-cardiogram, showed that the earlier of the two waves occurred during atrial systole, indicating hypertrophy of the right atrium, and the latter during the ejection phase of ventricular systole. A positive systolic wave similar to the second wave has been described in tricuspid incompetence (Muller and Shillingford, 1954). The blood pressure was 120/90. The apex beat was felt in the fifth left intercostal space 10 cm. from the mid sternal line and right ventricular pulsation in the third and fourth left interspaces. A systolic murmur (grade III) was loudest at the tricuspid area. In the same area there was a rather clicking sound in diastole. The phonocardiogram shows that this sound occurred 0·18 sec. after the beginning of the second sound, simultaneously with the base of the Y descent of the jugular venous pulse, i.e. later than a third heart sound is usually found. The systolic murmur extended throughout systole and was continuous with a short early diastolic murmur, which followed immediately on a split second sound. Such an early diastolic murmur has been described in tricuspid incompetence (Messer *et al*, 1950).

There were large P waves in leads II and aVF of the electrocardiogram and tall R waves in leads aVR and V1 (10 mm.), indicating much hypertrophy of the right ventricle. Cardiac catheterization showed that there was hypertension in the pulmonary artery and right ventricle. The mean pressure readings, all expressed in mm. of mercury above a plane 5 cm. behind the manubrium sterni, were (1) pulmonary "capillary" 4 mm. Hg; (2) main pulmonary artery 52 mm. Hg; (3) right ventricle 36 mm. Hg; (4) right atrium 5 mm. Hg, and (5) superior vena cava 5 mm. Hg. The oxygen content of samples of blood from the right heart, estimated by the method of Roughton and Scholander (1943), were (1) pulmonary artery 13·2 vol., (2) right atrium 12·9 vol., and (3) superior vena cava 12·9 vol., each per 100 ml.

A femoral artery blood sample contained 18·5 vol. per cent of oxygen. Hæmoglobin was 14·3 g. per 100 ml. and arterial oxygen saturation 96 per cent. Oxygen consumption was 210 ml. a minute and cardiac output 4 litres a minute.

Total pulmonary resistance, calculated from the formula,

$$\text{Resistance (dynes/sec./cm.}^{-5}) = \frac{\text{Mean pulmonary artery pressure (mm. Hg)} \times 1332}{\text{Cardiac output (ml./sec.)}}$$

was 1040 dynes/sec./cm.$^{-5}$. Pulmonary arteriolar resistance, calculated similarly from

$$\frac{\text{Mean pulmonary artery pressure (mm. Hg)} - \text{pulmonary "capillary" pressure (mm. Hg)} \times 1332}{\text{Cardiac output (ml./sec.)}}$$

was 960 dynes/sec./cm.$^{-5}$. Although the validity of these calculations, particularly of the second, is debatable, it seems fair to conclude that the pulmonary vascular resistance was greatly increased and that most of the increase arose in the pulmonary arterial tree.

Several unsuccessful attempts were made to obtain arterial blood during exercise to determine if there was interference with oxygen diffusion. The procedure was found to be impracticable because the patient's severe locomotor disability did not allow him to perform an adequate amount of exercise.

Discussion

There is no doubt that this patient presented the typical history and clinical features of chronic dermatomyositis and that he had at no time presented the characteristic hidebinding of "scleroderma."

The outstanding findings in the cardiovascular system were hypertension in the pulmonary artery and right ventricle, and great hypertrophy of the right heart. The normal pulmonary

" capillary " pressure excluded a lesion in the left side of the heart (such as mitral stenosis or constrictive pericarditis) as the cause of the pulmonary hypertension. There was no sign of a left-to-right intracardiac shunt or other evidence of a congenital defect of the heart; also, cardiac enlargement developed along with the dermatomyositis.

The only evidence of a valvular lesion pointed to tricuspid incompetence, which cannot explain pulmonary hypertension of this degree. Fibrosis of the myocardium leading to congestive cardiac failure has been described in scleroderma (East and Oram, 1947). None of the findings in the present case indicated that the cardiac dysfunction was due to myocardial damage of this kind. Emphysema was excluded by the respiratory function tests.

The only adequate explanation of the pulmonary hypertension and hypertrophy of the right heart appears to be a process of narrowing or occlusion of the smaller branches of the pulmonary arterial tree, the result of degenerative and proliferative changes in the vessel walls. There is some support for this view in the contrast between the enlarged main pulmonary artery branches and the somewhat inconspicuous peripheral vessels seen on the X-ray of the chest. This would then appear to be an example of the " vascular fibrosis " in the lungs described by Spain (1950). Right ventricular hypertrophy associated with such obliterative disease in the pulmonary arteries has been previously demonstrated in pulmonary schistosomiasis (Shaw and Ghareeb, 1938) and in carcinomatous infiltration of the lung vessels (Morgan, 1949).

Wood (1952) mentions polyarterities nodosa and disseminated lupus erythematosus as causes of block of the pulmonary circulation. In a recent comprehensive review of pulmonary changes in diffuse collagen diseases (Ellman and Cudkowicz, 1954) the authors suggest that the pulmonary arterial changes in this group are due to interference with tissue nutrition by deprivation of the only arterial blood supply available to the supporting structures of the lungs—the bronchial arteries. It seems at least as probable that the pulmonary arteries are affected primarily.

Summary

A case of dermatomyositis with severe pulmonary hypertension and hypertrophy of the right heart is described.

It is concluded that the pulmonary hypertension and hypertrophy of the right heart are the result of degenerative and occlusive changes in the smaller branches of the pulmonary arterial tree.

We acknowledge our gratitude to Dr. T. E. Anderson and Dr. R. J. Duthie for encouragement and for permission to publish this case and to Dr. C. D. Needham for the respiratory function tests.

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RHEUMATIC MITRAL STENOSIS AND AORTIC INCOMPETENCE IN A CASE OF DEXTROCARDIA WITH SITUS INVERSUS

BY

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From the Nilratan Sircar Medical College, Calcutta

Dextrocardia with situs inversus is not common and rheumatic valvular lesions in such cases are rare (Table I). It is considered that the circumstances of the case now described are worthy of record.

TABLE I

REPORTED CASES OF RHEUMATIC HEART DISEASES IN DEXTROCARDIA WITH SITUS INVERSUS

Author	Age	Sex	Age at first rheumatic attack (years)	Type of valvular lesion
Owen (1911)			—	Mitral stenosis
Pavel (1933)	29	M	7	Aortic incompetence
Abbott and Russek (1942) ..	43	M	?	Aortic stenosis
Pasternack (1942)				
Silberstein and Steinberg (1943)	33	F	13	Mitral incompetence and stenosis
Parson (1945)	24	F	21	Combined aortic and mitral lesion
Panek (1948)	45	F	9	Mitral incompetence and stenosis
Bleyer and Saphir (1953) ..	36	F	18	Mitral incompetence and stenosis
Berkowitz and Likoff (1954) ..	32	F	—	Mitral stenosis

Case History

A married girl, aged 14 years, was admitted to Nilratan Sircar Medical College Hospital with the history of continued fever for eight days. She had previously suffered from continued fever for about a month and was afebrile for a fortnight before she had this relapse. The patient had no cardiac symptoms. She suffered from rheumatic fever at the age of seven. Menstruation started at the age of twelve.

Physical examination revealed a thin, under-developed and slightly anæmic girl. She had no œdema, cyanosis, nor clubbing. Carotid pulsations were vigorous. The pulse rate was 120 a minute, regular and of water-hammer type. The blood pressure was 100/48; temperature 102° F. and respiration 26 a minute. The point of maximum cardiac impulse was localized at the right fifth intercostal space 1·25 cm. external to the right midclavicular line. At this area the first sound was loud and an early diastolic and a mid-diastolic rumbling murmur were heard. A blowing early diastolic murmur was heard at both second intercostal spaces close to the sternum, being conducted along the right border of the sternum to the apex of the heart. The pulmonary second sound was accentuated. The gastric resonance was found on the right side. The remainder of the examination was normal. The patient was afebrile on the seventeenth day of illness and left the hospital after five weeks.

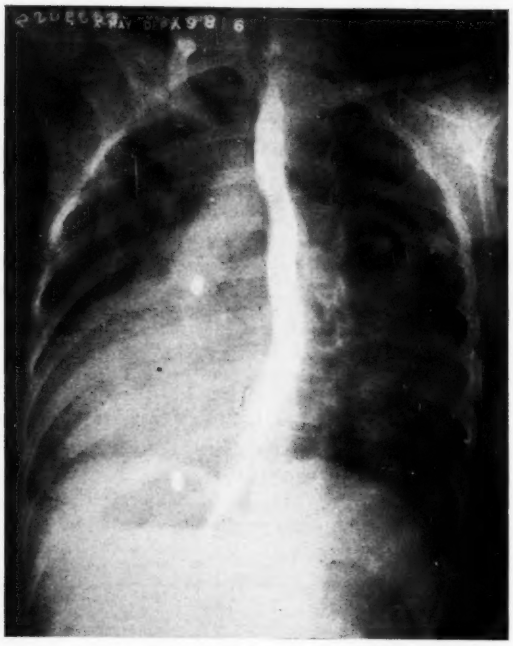

FIG. 1.—Teleradiogram of the heart in the left anterior oblique position, showing dextrocardia with situs inversus and enlargement of left auricle and left ventricle.

Investigations. Widal test was positive to TH in 1/125 and to TO in 1/83 on the ninth day of relapse of enteric fever. The Wassermann reaction of the blood was negative. X-rays of the heart showed dextrocardia with enlargement of left atrium and left ventricle (Fig. 1) and those of the skull absence of pneumatization of the frontal sinuses. Electrocardiograms showed the inversion of all the complexes in lead I and the interchanging of leads II and III characteristic of dextrocardia, and left axis deviation.

Summary

A case of rheumatic mitral stenosis and aortic incompetence complicating dextrocardia with situs inversus in a fourteen-year-old girl is reported. The patient was admitted to the hospital for treatment of a relapse of enteric fever and the cardiac findings were incidental.

We are grateful to Dr. A. K. Dutta Gupta, Principal-cum-Superintendent, Nilratan Sircar Medical College and Hospitals for permission to report the case, and to Dr. B. Bhattacharya for drawing our attention to the case.

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VENTRICULAR SEPTAL DEFECT SIMULATING PATENT DUCTUS ARTERIOSUS

BY

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The continuous machinery murmur heard over the pulmonary area is generally evidence of a patent ductus arteriosus, but there are exceptions when the murmur is due to congenital aortic septal defect (Gross, 1952; Gasul *et al.*, 1951), to perforated aortic sinus into the right ventricle (Jones and Langley, 1949; Wood, 1950), or to rupture of an aortic aneurysm into the pulmonary artery (White *et al.*, 1941; Porter, 1942).

The case reported below with a high ventricular septal defect just below the aortic valve, complicated by aortic regurgitation from distortion of an adjoining valve cusp, provides another example. This combination was described by Laubry and Pezzi (1921) and Laubry *et al.* (1933). In describing Eisenmenger's complex, Taussig (1947) stated that the aortic cusp which lies above the ventricular septal defect is often abnormally large and deep and sometimes at a lower level than the other two cusps; aortic insufficiency frequently occurs and at necropsy a scarred valve is found.

The adjoining cusp may herniate into the right ventricle through the ventricular septal defect giving rise to severe aortic incompetence and a clinical picture resembling a patent ductus. Such cases were recorded by Allen (1941), Hurst and Schemm (1948), and Soulié *et al.* (1949). Ash and Murphy (1950), Ascenzi *et al.* (1951), and Baylis *et al.* (1955) recorded cases having similar clinical features where the aortic cusp had herniated through the defect into the right ventricle. Some patients in whom a high ventricular septal defect lay in such a position that the medial cusp of the aortic valve was incompletely supported, and hence collapsed from time to time giving rise to aortic insufficiency, have been noted by Gross (1953). In reporting 60 cases with isolated ventricular septal defect, Wood *et al.* (1954) diagnosed two more with marked aortic incompetence, one of which died suddenly and was found to have a deformed anterior aortic cusp which had partly prolapsed into the defect of the ventricular septum. Several of these authors concluded that the syndrome of ventricular septal defect with aortic incompetence is apt to be mistaken for a patent ductus and may lead to a profitless and dangerous operation.

Case Report

A Chinese girl, aged 14 years, was admitted to the General Hospital, Singapore some hours after the onset of severe retrosternal pain which had come on suddenly that day. While alighting from a bus on her way home from school, she suddenly developed severe gripping pain behind the sternum which radiated upwards to both sides of the neck and downwards along the inner side of the left arm, and difficulty in breathing. She managed to walk the few yards home and went to bed. There was no history of similar attacks in the past; her previous health was good and her parents were not aware of the presence of any heart disease prior to this admission.

Physical examination showed a well-built young girl who appeared to be in a state of shock from severe pain. She was pale and breathless, with a cold clammy skin; the pulse which was collapsing in character was rapid but regular at 150 a minute. The systolic blood pressure was 84 mg. Hg but the diastolic pressure was not obtainable, the sounds remaining audible until the pressure reached zero. There was no cyanosis and no visible pulsations in the neck. The cervical veins were not engorged and there was no œdema.

The apex beat was felt 10 cm. from the midline in the fifth left intercostal space and was not forceful. In the second left intercostal space parasternally a continuous thrill, which filled the whole of systole and

diastole, was easily felt. Over the same area a loud, rough, and continuous " machinery " murmur with systolic accentuation was heard; it was transmitted over the entire præcordium and obscured both heart sounds. Examination did not reveal any other abnormality.

The diagnosis made at this stage was of patent ductus arteriosus, but the retrosternal pain was difficult to explain and was thought to be due to cardiac ischæmia resulting from paroxysmal auricular tachycardia. This, however, was not substantiated by the electrocardiogram which showed a sinus tachycardia of 150 a minute and left ventricular strain. She showed no response to treatment and died eight hours after admission to hospital.

Necropsy

Careful dissection failed to disclose a patent ductus and no ligamentum arteriosum was found.

The heart weighed 150 g. and was not generally enlarged though there was slight hypertrophy of both ventricles. Directly below the attachment of the anterior aortic cusp was a circular ventricular septal defect, about 1 cm. in diameter, which was almost completely occluded by a pouch-like dilatation of the base of this cusp (Fig. 1). The pouch, which also measured about 1 cm. in diameter, had collapsed and protruded through the septal defect appearing in the right ventricular cavity as a thin membrane just below the pulmonary valve (Fig. 2). A rupture of this pouch at its apex was demonstrated by passing a probe through it from the left to the right ventricle. The trivial resistance offered by this displaced cusp to the column of blood returning in diastole must have resulted in gross aortic insufficiency. None of the cusps showed any evidence of sclerosis or of bacterial endocarditis: there was no widening of the commissures nor dilatation of the aortic ring. The orifice of the right coronary artery was higher than usual being above the level of the upper border of the deformed cusp; both coronary vessels were patent. The other valves and the aorta and pulmonary artery showed no abnormality. Examination of the lungs, liver, kidneys, and spleen showed only congestive changes. The skull was not opened.

Discussion

The diagnosis of patent ductus arteriosus is made with a high degree of accuracy by the detection of a continuous machinery murmur over the pulmonary area but in 4 of the cases quoted thoracotomy for ligation of a patent ductus was performed when there was a high ventricular septal defect with a deformed aortic cusp. It would therefore appear that this possibility must be taken

FIG. 1.—Photograph of the left ventricle, showing the anterior aortic cusp prolapsed into the ventricular septal defect.

into consideration in the elucidation of what seems to be a characteristic continuous murmur in the pulmonary area, and cardiac catheterization studies performed in those cases where the murmur does not have the truly continuous quality of a patent ductus. However, even then the data may be insufficient to differentiate a patent ductus with free pulmonary regurgitation from a high ventricular septal defect of the type described in this paper unless intracardiac pressure recordings are made, as in the case reported by Morgan and Burchell (1950).

FIG. 2.—Photograph of right ventricle, showing the prolapsed anterior aortic cusp below the pulmonary valve. The rupture of the cusp at its apex is evident. (The specimen had been fixed in formalin when the photograph was taken.)

The prognosis in patients with ventricular septal defect is often considered to be good, but when there is an associated defect of the adjacent aortic cusp the prognosis is far more serious; there is an added strain on the heart from aortic insufficiency resulting in early or sudden cardiac failure.

In the case described above, the prolapse of the right aortic cusp had caused severe incompetence of the aortic valve, but this must have been a recent episode because none of the cusps showed any evidence of thickening or fibrosis. The præcordial pain was thought to be aortic in origin; the prolapse of the cusp probably caused acute tension of the wall of the aorta at its site of attachment. The presentation of a case with severe cardiac pain has so far not been recorded to the writer's knowledge.

Summary

A case is reported in which a continuous murmur in the pulmonary area led to a diagnosis of patent ductus arteriosus but at necropsy a high ventricular septal defect with prolapse of the adjoining aortic cusp through the defect was found. Attention is drawn to the uncommon presentation

with cardiac pain and to the poor prognosis in this type of ventricular septal defect with a deformed aortic cusp.

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ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

Cardiac Catheterization in Congenital and Acquired Heart Lesions. (Der Herzkatheterismus bei angeborenen und erworbenen Herzfehlern.) OTTO BAYER, FRANZ LODGEN, H. HELMUTH WOLTER. 1954. Georg Thieme Verlag, Stuttgart. 191 pages. 111 illustrations. DM 36.

Catheterization of the heart is described in both acquired and congenital lesions. In the course of five years the workers at Düsseldorf have examined some eight hundred cases. There is a full account of the methods of computing the areas of the pulmonary and mitral openings; it would have been valuable to have had more actual consideration of the value and accuracy of these procedures. Nearly all the various congenital defects have been described. All this is well done. There are good skiagrams and the pressure curves are mostly clear. The standard and chest leads are given in the cardiograms; some are marred by interference. The diagrams of the circulation are not so clear as they might be. The acquired defects are tricuspid incompetence, pulmonary incompetence and mitral lesions. There is a full list of references, not well-linked to the text. Altogether this work presents well the information to be obtained by modern methods of cardiac catheterization, and can be recommended. The information is well set out and easily found. *Terence East*

Angina Pectoris. W. H. HAUSS. 1954. Georg Thieme Verlag, Stuttgart. 394 pages. 127 illustrations. DM 59.40.

Angina Pectoris by Prof. W. H. Hauss starts with an historical survey and the name of William Heberden, but Allan Burns hardly has full credit for his brilliant theory. The pathological and clinical aspects are fully considered; the familial incidence is stressed. It is interesting to read that infarction in 1937 was 0·3 per cent in Frankfurt, and in 1953 it had risen to 2·3 per cent of total inpatients. The cardiograms are clear and plentiful. It would have been easier to study them if fewer complexes had been shown, and the arrangement had been across the paper. Neb's triangle seems to replace the unipolar limb leads. In the treatment section there are many drugs mentioned, but no detailed account of the relative values is given. This rather mars the book throughout; there is much information, but not enough of summary and conclusion to make it easily assimilated. The paper is good and there is a full index, but the references omit many papers that are familiar enough outside Germany. *Terence East*

Lehrbuch der Auskultation und Perkussion. K. HOLLDACK. 1955. Georg Thieme Verlag, Stuttgart. 195 pages. 83 illustrations. DM 27.

This " Text Book of Auscultation and Percussion " discusses the older methods of physical examination in the light of modern knowledge. The title is hardly a good indication of the contents, for inspection is included too, and comes first—and palpation comes last. At least, this is the first arrangement as regards the head and neck. In the examination of the thorax, inspection and palpation come first. The suggestion is made that percussion is but little used in the Anglo-Saxon lands, particularly as regards the heart. But here it seems odd to us that anyone should use the percussion hammer and pleximeter nowadays. Too little is given, in small print, about funnel sternum. As one of the two procedures that form the title of this book has little value in abdominal examination, this part of the body received small attention. The nervous system gets more. Very little is said about the palpation of the arteries; the method of examining the liver (Fig. 60) is curious. Do the finger tips really appreciate temperature better than their backs? It is doubtful whether the student of clinical medicine in this country has much to learn from this book.

Terence East

Cardiac Auscultation. J. SCOTT BUTTERWORTH, M.D., Associate Professor of Medicine, New York University Post-Graduate Medical School; MAURICE R. CHASSIN, M.D., Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School; ROBERT MCGRATH, M.D., Associate Professor of Clinical Medicine, NewYork University Post-Graduate Medical School. Grune & Stratton. Pp. 105. $4.50.

This is a short book, well illustrated and written and nicely reproduced. The findings of auscultation are described very clearly and are demonstrated by phonocardiograms. This should be a valuable method of teaching and is already used by many clinicians when they draw their auscultatory impressions. Therefore one approaches this book with a good deal of hopeful anticipation and, while its principle is commended, it is unfortunate that there are some criticisms to be made. The outlook tends to be anatomical and the book would be improved for teaching purposes if there were more hæmodynamic principles. The current impressions that auricular and third heart sounds are " filling sounds " is not mentioned and gallop rhythm is said to occur almost invariably with heart rates of 100 or more, so that by this definition only summation gallop can be considered. Each illustration consists of a single phonocardiogram without time-marker or reference tracing. This contributes to clarity but has resulted in failure to show some valuable clinical points. The aortic and pulmonary components of the second sound cannot be identified, and there is no description of the wide splitting of the second sound in the pulmonary area which is so useful in the diagnosis of atrial septal defect and bundle-branch block. There is no mention of the European literature on auscultation since Laennec, perhaps with purpose, since it is stated that the monaural wooden stethoscope is still commonly used in European countries.

Thus, the clinical side is seen to be disappointing but the discussion of the principles of hearing and of the stethoscope at the beginning of the book is excellent and is recommended. *Aubrey Leatham*

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

An AUTUMN MEETING of the British Cardiac Society was held at the Royal Society of Medicine, 1 Wimpole Street, London, on Friday, October 14, 1955. The Chairman, CRIGHTON BRAMWELL, took the Chair at 9.30 a.m.; 123 members and 27 visitors were present.

PRIVATE BUSINESS

1. The minutes of the last Annual General Meeting having been published in the Journal (**17**, 573, 1955) were taken as read and confirmed.
2. The Chairman spoke of the loss that the Society and British Medicine had sustained in the deaths of the Right Hon. Lord Horder, Dr. A. J. Wilson, and Dr. I. McPherson, and members stood in silence.
3. Sir William Hume was unanimously elected as an *Honorary Member* of the Society, with acclamation.
4. Sir John Parkinson's term as *President* expiring at the beginning of the next Annual General Meeting, he having been elected in May, 1952, Maurice Campbell was nominated as the new *President* to take office at the Annual General Meeting, 1956.
5. Samuel Oram's term of office expiring at the beginning of the Annual General Meeting, 1956, Patrick Mounsey was elected as the new *Honorary Secretary and Treasurer*.
6. The names forwarded to Dr. K. E. Grewin, the Secretary-General of the Second European Congress of Cardiology, to represent this country in the various panel discussions and round-table conferences to be held at the Congress, which is to take place in Stockholm from September 10 to 14, 1956, were reported.

SHORT COMMUNICATIONS

MITRAL VALVOTOMY—A PROGRESS REPORT

By R. W. D. TURNER. Many groups reported their early experience with the surgical treatment of mitral stenosis, but there has been no progress report from this country. We have reviewed the first 250 patients operated upon from one medical unit over a period of 4½ years, none less than 6 months ago.

The cases have been analysed in relation to various factors that may influence the result, including age, rhythm, heart size, heart failure, clot, calcification, and associated mitral incompetence or aortic valvular disease.

Brief reference was made to physical signs, special methods of investigation, instrumental aids to valvotomy, and subsequent re-fusion.

THE ASSESSMENT OF THE SEVERITY OF MITRAL STENOSIS BY THE DELAY IN THE FIRST HEART SOUND AND THE OPENING SNAP OF THE MITRAL VALVE

By BERTRAND WELLS. One hundred patients with mitral stenosis have been assessed by measuring the delay in the first heart sound, and the interval between the second heart sound and the opening snap of the mitral valve. An operation of mitral valvotomy has since been performed on each of these patients, and the size of the mitral orifice and the pressure gradient across the mitral valve has been recorded. The correlation between the pre-operative assessment and the operative findings is close, and enables the mechanism of formation of the heart sounds to be clarified.

Further information on the mechanism of formation of the first heart sound and the opening snap is obtained from phonocardiograms taken during operation, with synchronous pressure tracings from the left atrium and the left ventricle.

This study demonstrates that the phonocardiograph is of value in selecting patients suitable for mitral valvotomy.

THE CONTRIBUTION OF TRICUSPID INCOMPETENCE TO RIGHT VENTRICULAR OUTPUT IN CONGESTIVE HEART FAILURE

By PAUL KORNER (*introduced*) and JOHN SHILLINGFORD. Studies of the right atrial pressure and flow curves in patients with cardiac failure show that with a raised venous pressure considerable tricuspid regurgitation may occur. The presence of this incompetence throws an increased load on the right ventricle for

a given cardiac output. With the development of the dye dilution technique for the quantitative estimation of regurgitant flow, it has now been possible to gain further knowledge of the effect of incompetent valve lesions on the cardiac output and its relation to heart failure.

A quantitative estimation of the amount of backflow through incompetent tricuspid valves has been correlated with the clinical and necropsy findings in 14 patients, 13 of whom were in congestive heart failure. With the development of functional tricuspid incompetence in congestive heart failure the right ventricular stroke output remains higher than in normal subjects in spite of a low forward cardiac output, the discrepancy being due to regurgitant flow.

Exercise tends to increase the regurgitant flow at the expense of the forward cardiac output although the total right ventricular output may remain the same or rise; rest has the opposite effect.

These results correlate with the clinical and necropsy findings and offer an explanation for the phenomenon of " low fixed cardiac output " in some patients with congestive cardiac failure.

The Murmurs of Patent Ductus Arteriosus

By Catherine Neill (*introduced*) and Patrick Mounsey. A clinical and phonocardiographic study has been made of the murmurs in 100 consecutive patients with patent ductus, in whom the diagnosis was subsequently confirmed at operation. The murmurs were of two types, that of uncomplicated patent ductus and that of patent ductus complicated by severe pulmonary hypertension. In the latter the diastolic element of the murmur tended to disappear while the systolic murmur was often insignificant. A functional mid-diastolic murmur, preceeded in some cases by a sound resembling a soft opening snap, was seen in the presence of a large shunt, and both the murmur and sound disappeared after ligation of the patent ductus. This observation suggested that the " snap " as well as the murmur might be functional and due to increased blood flow through the mitral valve.

In the differential diagnosis from other continuous murmurs, the timing of the murmur appeared important, although in most cases the site of the maximum intensity indicated the nature of the lesion. The timing of the murmurs of patent ductus, of bronchial arteries, of systemic and pulmonary arteriovenous fistulæ, and of venous hums were compared, and it was seen that the murmur became increasingly delayed as the distance of its site of origin from the heart increased. In rarer congenital lesions, such as aortic septal defect or coronary-pulmonary fistula, the site and timing of the murmur were sometimes atypical of patent ductus, but in other patients no certain differentiating points were found.

The Auscultatory and Phonocardiographic Signs of Atrial Septal Defect

By Ian Gray (*introduced*) and Aubrey Leatham. Published in full *Brit. Heart J.*, **18**, 1956.

Closure of Atrial Septal Defects—a Method of Treatment

By F. Ronald Edwards. Atrial septal defects can be closed by suture. A method is described whereby the defect is sutured through the wall of the right atrium, the edges of the defect being directly opposed and the atrial wall fixed over the sutured object as a strengthening patch. The operation is performed under tactile control. No hypothermia is required.

The operation is best performed in the young, and before severe failure and gross cardiac enlargement are established.

Of the 14 cases explored, 13 have had the operation performed, and a satisfactory result obtained in 11 cases. Two died post-operatively; one, an unsuitable advanced case, from cardiac failure, and the other from a technical error producing an aortico-atrial fistula.

Cine-angiocardiography with an Image Intensifier

By R. Astley (*introduced by Clifford Parsons*). The conventional method of cine-radiography is photography of the fluorescent screen image: this involves high dosage of radiation to the patient and heavy loading of the X-ray apparatus. The advent of the image intensifier has reduced these hazards and provided a practical method of cine-radiography. Limitations are the restricted field area and the standard of definition, which is inferior to that of an ordinary radiograph. An advantage is that the gain of a sense of movement aids interpretation of the results.

A short 16-mm. film, made up of prints from cine-angiocardiograms, was shown to demonstrate the possibilities of the method.

A Proposed Clinical Method of Investigating the Elasticity of Large Arteries

By James Conway (*introduced*) and K. Shirley Smith. A method of determining the state of the elastic tissue of the large arteries is being studied; it depends upon the delivery from the heart at each beat of the same volume of blood at different levels of diastolic pressure, changes in pulse pressure thus produced being an indication of loss of arterial elasticity. If the arterial reservoir is reasonably elastic at the normal diastolic level of pressure, then reduction of pressure without change in stroke volume would leave the pulse pressure unchanged.

In order to produce these theoretical conditions, patients and volunteers have been used in observations in which the blood pressure and pulse pressure was recorded by a condenser manometer from the brachial artery, and the blood pressure was reduced by inhalation of amyl nitrite. It was assumed that amyl nitrite did not have an immediate effect upon stroke volume and did not influence the elasticity of the large arteries while it produced dilatation of the small muscular vessels. Reduction of pressure was thus produced and the pulse pressure could be studied for a limited number of heart beats, until tachycardia ensued and the assumption concerning stroke volume no longer held. Predictions from this theory have been examined and upheld in 10 young student volunteers all of whom have been shown to have elastic arteries. Thirty patients with hypertension have been studied and have been found to fall into two groups: (1) those in whom the pulse pressure does not fall with the reduction of diastolic pressure (i.e. those with elastic arteries), and (2) those with a considerable fall in pulse pressure and according to the test with inelastic arteries. Many of the " inelastic group " have clinical evidence of arteriosclerotic hypertension and many of the " elastic group " are young patients with severe hypertension. There are very few contradictions between advanced clinical signs and the findings in these tests.

The Heart in Disseminated Lupus Erythematosus

By W. Brigden, E. G. Bywaters, and (*introduced*) M. Lessof and I. Ross. The cardiac manifestations of disseminated lupus erythematosus were investigated in 30 patients, and 11 of these were examined at necropsy. Acute or subacute pericarditis was recognized clinically on some occasion during the disease in 50 per cent, but electrocardiographic changes compatible with pericardial disease occurred in 85 per cent, and evidence of past pericarditis occurred in all of the necropsy cases. Myocarditis was difficult to recognize clinically, but there was evidence that extensive myocardial disease was a factor in the development of heart failure in patients who had systemic hypertension. Definite clinical evidence of valvulitis occurred in only 5 cases and two of these developed mitral systolic and diastolic murmurs while under observation. One patient died of bacterial endocarditis. At necropsy 5 cases had endocarditis; the mitral valve was affected in all, the tricuspid valve in three, and one had evidence of slight aortic valvulitis.

The Effects of Penicillin Treatment on the Histological Lesions of Syphilitic Aortitis

By B. E. Tomlinson (*introduced by W. G. A. Swan*). The criteria used in this communication for the diagnosis of active syphilitic aortitis were stated.

The histological changes in the aorta in 23 cases of syphilitic aortitis treated with varying amounts of penicillin were described. These findings were compared with those of a control series of cases of syphilitic aortitis in which penicillin had not been given. Slides of the lesions were shown. The changes in the treated cases in relation to the period of survival after treatment, and the time needed for syphilitic lesions to resolve, were discussed.

The conclusion was reached, that in this series, there was no convincing evidence that penicillin is usually effective in the treatment of established syphilitic aortitis.

Coronary Heart Disease in the Presence of Pulmonary Disease

By Arthur J. Thomas. Pulmonary disease and coronary artery disease are frequently found together in necropsies on coalworkers. To study this problem in the population it is necessary to verify the clinical diagnosis of coronary heart disease. To this end a correlation of the clinical and post-mortem findings has been made in 51 coalworkers with severe pulmonary disease, either pneumoconiosis or chronic bronchitis and emphysema.

27 cases had clinical and post-mortem evidence of coronary heart disease.

17 cases queried clinically as having other heart disease in addition to pulmonary disease were not confirmed at necropsy as having coronary heart disease.

7 cases with severe coronary artery disease at necropsy had not been so regarded during life, but had severe pulmonary heart disease.

27 *cases*	Average age 62 (46–74) years	
Necropsy findings	Cardiac infarction: 11	Severe coronary artery disease: 16
Heart weight (mean)	455 g. (340–700 g.)	305 g. (220–400 g.)
Cardiac pain	7	5
B.P. over 160/100	3	2

Electrocardiographic analysis of the 27 *cases*		Cardiac pain
Pulmonary heart disease	5	
Cardiac infarction	6	4
Right bundle-branch block with S–T segment change	4	1
S–T trough depression I and V6 ..	5	1
Right axis with S–T trough depression in III and V6	2	1
QIII abnormal	2	0
aVL abnormal (also auricular fibrillation in I)	2	1
Left axis deviation and auricular fibrillation	3	2
L.A.D. and auricular tachycardia ..	1	1
L.A.D. and low blunt TI	1	1
L.A.D. only	1	(L.V. enlarged)

A high degree of left axis deviation, a qR in aVL with T inversion, and trough depression of S–T in V6 were not present in comparable cases of pure pulmonary disease. The lesser electrocardiographic signs of myocardial injury (Evans and McRae, 1952) have been valid in this series, and were present in 8 cases, 5 without recognized cardiac pain. Auricular fibrillation has been extremely rare in pure pulmonary heart disease, but was present in four cases with both diseases. It has been possible to distinguish cardiac pain from the sharper and more variable pleuro-pulmonary pain correctly 12 times but incorrectly once. The more severe the ischæmic heart disease the heavier the left ventricle (Harrison and Wood, 1948). Left ventricular prominence at cardioscopy may be supporting evidence of coronary heart disease.

Analysis of 17 cases of severe pulmonary disease with minimal coronary artery disease at necropsy shows that 5 without other electrocardiographic abnormality were pure pulmonary disease; the 12 with unexpected cardiographic abnormality had respectively, myocardial fibrosis of unknown origin (2), pericarditis (3), hypertensive disease (2), paroxysmal tachycardia (2), heart block (? digitalis effect) (1), right bundle-branch block (1) and one unexplained. The mean heart weight was 412 g. (300–572 g.). Three of these only, viz. myocardial fibrosis (2) and right bundle-branch block (1), could appear incorrectly in the first group on clinical findings.

These methods can be applied to the detection of coronary heart disease in a group of people without producing a false high incidence. The results in a group of 110 coalworkers not seriously ill but complaining of some respiratory disability was shown.

An analysis of the relationship of pulmonary disease and coronary heart disease did not show any direct relationship between them.

The Anatomical Changes in Rheumatic Tricuspid Valve Disease

By Arthur Hollman (*introduced by Dr. Kenneth Harris*). The normal anatomy and function of the tricuspid valve were described. The orifice points towards the nearby outflow tract of the right ventricle being set roughly at right angles to it. Valve closure is effected mainly by apposition of the atrial surfaces

of the cusps. The mitral orifice by contrast is comparatively flush with the wall of the left ventricle and does not point towards the outflow tract. Mitral valve closure is more efficient than tricuspid valve closure.

Twenty-one pathological specimens of rheumatic tricuspid valve disease have been studied with the main objects of determining the probable function of the stenosed tricuspid valve and the feasibility of valvotomy. Five specimens had well-marked stenosis with orifices 1·5 cm. in length or less and of these probably only one was a competent valve. The detailed anatomy of these specimens was described with particular reference to commissural fusion and the probable function of the valves after valvotomy.

Of the sixteen larger valves, also fully described, several were grossly incompetent.

In rheumatic disease of the tricuspid valve incompetence is frequently associated with stenosis. There are anatomical reasons for this.

The Electrocardiogram in Induced Hypothermia

By Peter R. Fleming (*introduced by Charles Baker*). The study comprises an analysis of electrocardiograms recorded during experimental hypothermia in dogs and during eighteen operations performed using hypothermia at Guy's Hospital.

The changes seen were essentially similar in dogs and in men except that the dogs were resistant to the production of auricular fibrillation which occurred frequently in the human patients. This arrhythmia rarely occurs during cardiac surgery at normal temperatures. In this series its occurrence seemed to indicate a good prognosis.

In all cases changes due to the anæsthetic or the operation have been eliminated as far as possible by comparison with records at similar operations at normal temperatures.

All cases showed bradycardia. This was associated with a lengthening of the S–T interval, greater than would have been expected from the change in rate alone. The P–R interval (where present) and the QRS were not consistently prolonged, but in some cases a characteristic deformity of the QRS–ST junction appeared. This was seen more frequently in dogs and consisted of a notch on the downstroke of the R wave which deepened until the whole complex became biphasic; the secondary wave sometimes exceeded the R wave in height. It is not certain whether the second wave is part of the QRS complex and represents impaired conduction or whether it is the first part of the S–T segment and represents a current of injury. This point was discussed.

ABSENCE OF THE LEFT PULMONARY ARTERY IN FALLOT'S TETRALOGY

BY

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Where the right or left branch of the pulmonary trunk (R.P.A. or L.P.A.) is absent, the main pulmonary vessel, after arising from the right ventricle, continues in an even curve to the hilum of one lung: there is no bifurcation of the main trunk and no pulmonary artery passing to the hilum of the other lung. Instances of this in association with Fallot's tetralogy have been reported. We are not considering here cases with absence or atresia of the main pulmonary trunk or absence of one pulmonary artery associated with complete agenesis of the ipsilateral lung.

Fraentzel (1868) was the first to describe a case of absence of the R.P.A. Four further cases were described during the next 73 years (Döring, 1914; Müller, 1927; Ambrus, 1936; and Miller, 1937). The first example of absent L.P.A. was recorded by Thomas (1941) in an infant with Fallot's tetralogy. The majority of cases with absence of either R.P.A. or L.P.A. have been reported in the last 8 years. Blalock (1947 and 1948) encountered 9 examples in his series of 610 cases of cyanotic congenital heart disease with pulmonary stenosis. Other cases have been reported by Campbell (1948), Bret and Feroldi (1950), Donzelot *et al.* (1952), Jew and Gross (1952), Madoff *et al.* (1952), Lowe (1953), Campbell (1954), Flynn *et al.* (1954), Madoff (1954), Read (1954), and Steiner (1954). Findlay and Maier (1951) and Steinberg *et al.* (1952) each described two examples. Three cases were recorded by Maier (1954) of which Case 3 had been previously reported by Findlay and Maier in 1951. A further 3 were described by Wyman (1954), 5 by Nadas *et al.* (1953) and 6 by McKim and Wiglesworth (1954).

The total number of cases recorded with absence of the L.P.A. or R.P.A. is 46. In 6 of Blalock's (1947 and 1948) cases, however, it is not stated which branch of the pulmonary artery was missing, and in 2 of Wyman's (1954) examples, insufficient details of the cardiac abnormalities present were recorded for the purpose of this paper. Thus we are left with 38 cases for consideration. The patient of Sweet and White (1950) referred to by Findlay and Maier in 1951 has been quoted by some authors as an example of absent L.P.A., but has been omitted since there was a truncus arteriosus and no evidence of a pulmonary artery coming from the heart.

The observations in this paper followed the study of two cases of Fallot's tetralogy in which the L.P.A. was absent. There are reports of 18 similar cases; the L.P.A. was absent in 17 and the R.P.A. in the remaining case, but this was associated with dextrocardia and situs inversus (Nadas *et al.*, 1953). In 10 of these 17 cases, the diagnosis was confirmed at necropsy. McKim and Wiglesworth (1954) reported a case of Eisenmenger's complex (confirmed at necropsy) in which the L.P.A. was missing. In these 21 cases, 19 previously reported and 2 reported here, the L.P.A. was absent in all, if it is assumed that absence of the R.P.A. with dextrocardia is embryologically equivalent to absence of the L.P.A. with lævocardia. The cardiac lesion common to all was a defect in the development of the bulbus cordis, giving rise to lesions of the upper part of the ventricular septum and infundibulum of the right ventricle. This appeared to be associated more frequently with absence of the L.P.A. than could be accounted for by chance.

Nineteen reported cases in which absence of one or other branch of the pulmonary artery was associated with normal development of the bulbus cordis were collected for comparison. In 8 of these the heart was normal and in the remaining 11 (9 confirmed at necropsy) the lesion did not involve the bulbus cordis, the abnormality in the majority being confined to the great vessels (patent ductus arteriosus, 3 cases; coarctation of the aorta, 3 cases). In these 19 cases the R.P.A. was absent in 17, and the L.P.A. in the other 2. The frequency of absence of the R.P.A. in this group compared with that of the L.P.A. in the previous group suggested that there must be an embryological explanation for these findings.

The occurrence of right-sided aortic arch with Fallot's tetralogy has been recorded for over one hundred years (Corvisart, 1818), although it was not until 1936 that Bedford and Parkinson drew attention to the frequency of this association. More recently Taussig (1947) reported the incidence of right-sided aortic arch in these cases to be between 20–25 per cent. In 20 cases of Fallot's tetralogy with absence of the L.P.A. (our 2 and 18 reported previously) we have found a much higher incidence of right-sided aortic arch for this occurred in 12 of the 20 cases (60%).

The site of the aortic arch is stated in 16 of the 17 cases with absence of the R.P.A. In this group the heart was either normal or the lesion confined to the great vessels, but in no instance was a right-sided aortic arch recorded. This excludes the case of dextrocardia with Fallot's tetralogy mentioned above (Nadas *et al.*, 1953).

Discussion

The standard embryological diagrams derived from Rathke, show both pulmonary arteries sharing equally the proximal parts of the sixth (pulmonary) arches. Bremer (1902 and 1909), however, whose studies include human embryos, disagreed with the conventional view and produced evidence that the original symmetry of these arches was disturbed by absorption of the proximal part of the left arch (A, Fig. 1) into the truncus pulmonalis. The adult plan is reached (Fig. 2) with the absorption of the distal part of the right sixth arch (B, Fig. 1), the corresponding part of the left sixth arch becoming the ligamentum arteriosum (C, Fig. 1). Keibel and Mall (1912) agreed with Bremer's work which received further support from Congdon (1922). Thus, it appears that the right and left pulmonary arteries differ embryologically. The right sixth arch forms the proximal part of the R.P.A. (D, Fig. 1 and 2) while on the left side the corresponding structure has been absorbed so that the L.P.A. contains no part of the left sixth arch.

Bremer's work makes it possible to account for our findings, which cannot be explained if the conventional view of symmetrical development of the two pulmonary arteries is accepted. In cases where the development of the bulbus cordis is abnormal, it appears that the absorption of the left sixth arch (A, Fig. 1) is affected and that this in a proportion of cases leads to absence of the L.P.A. In the other group where the bulbus cordis has developed normally, it is more difficult to explain why the R.P.A. is absent in such a high proportion of cases. It is possible, however, at the time when the left sixth arch is normally absorbed, that in some cases the proximal part of the right sixth arch (D, Fig. 1 and 2), is also involved in the absorption process, thus eliminating an essential part of the R.P.A. and preventing development of this vessel. Meanwhile the L.P.A. will develop normally. This accounts for all cases recorded except two, where absence of the L.P.A. was associated with a normal heart.

The practical significance of this is that absence of the L.P.A. is generally associated with Fallot's tetralogy, while absence of the R.P.A. is found either with normal hearts or those in which the congenital lesion is confined to the great vessels.

Case Reports

Case 1. This girl, aged 6, was investigated at Middlesex Hospital in October, 1953. Cyanotic heart disease diagnosed at birth. Frequent squatting. Could walk only 50–100 yards at normal pace before dyspnœa forced her to stop.

Mentally normal. Moderate cyanosis and clubbing. Venous pressure normal. Pulse regular 90 a

minute. B.P. 115/80 mm. Hg. Heart enlarged. Cardiac impulse, right ventricular in character. Pulmonary systolic murmur, conducted to the right of the sternum, also heard over back but only on the right side. Second sound single.

Electrocardiogram, sinus rhythm, right ventricular hypertrophy of considerable degree (right axis deviation, vertical heart, tall R in V1, deep S in V6, T negative in V1 only). Hb. 127 per cent, 18·4 g., P.C.V. 60·5 per cent. Chest X-ray, slight cardiac enlargement, left-sided aortic arch, pulmonary artery

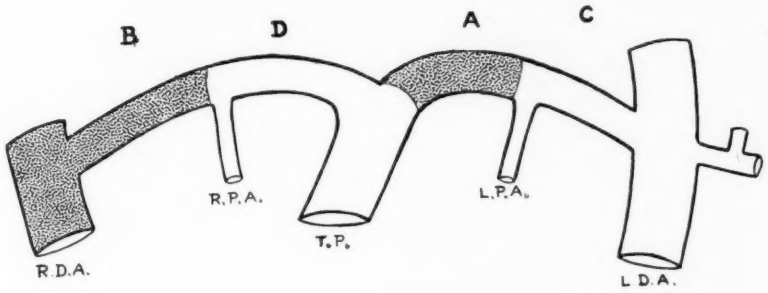

FIG. 1.—Diagram of the sixth (pulmonary) arch in the embryo. The shaded portions (A and B) are absorbed during development. A., Proximal portion of sixth (pulmonary) left arch. B., Distal portion of sixth (pulmonary) right arch and right descending aorta. C., Distal portion of sixth (pulmonary) left arch and left descending aorta. D., Proximal portion of sixth (pulmonary) right arch. R.D.A. and L.D.A., Right and left descending aorta. R.P.A. and L.P.A., Right and left pulmonary artery. T.P., Truncus pulmonalis.

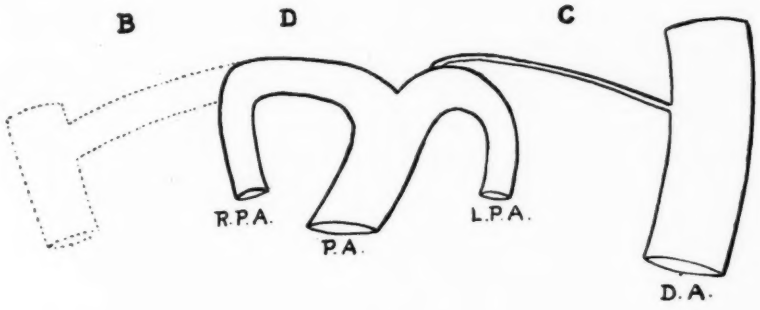

FIG. 2.—Adult pattern of the pulmonary arteries in man. P.A., Pulmonary artery. D.A., Descending aorta. For other letters see Fig. 1.

segment concave, and apex prominent and slightly elevated. Large R.P.A. and apparently small L.P.A. Angiocardiogram: large right ventricle, with simultaneous filling of aorta and small pulmonary trunk; stenosis of both pulmonary valve and infundibulum; R.P.A. very large and branches to the right upper and lower lobes almost aneurysmal. No trace was seen of the L.P.A.; there appeared to be a scanty bronchial arterial supply to the left lung, giving the appearances that simulated a small L.P.A. on the plain X-ray. The aortic arch was on the left and the vessels arising from it appeared normal (Fig. 3). Pulmonary veins were normal on the right, but none were seen on the left. Left atrium and left ventricle were outlined and the aorta was seen to refill with contrast medium.

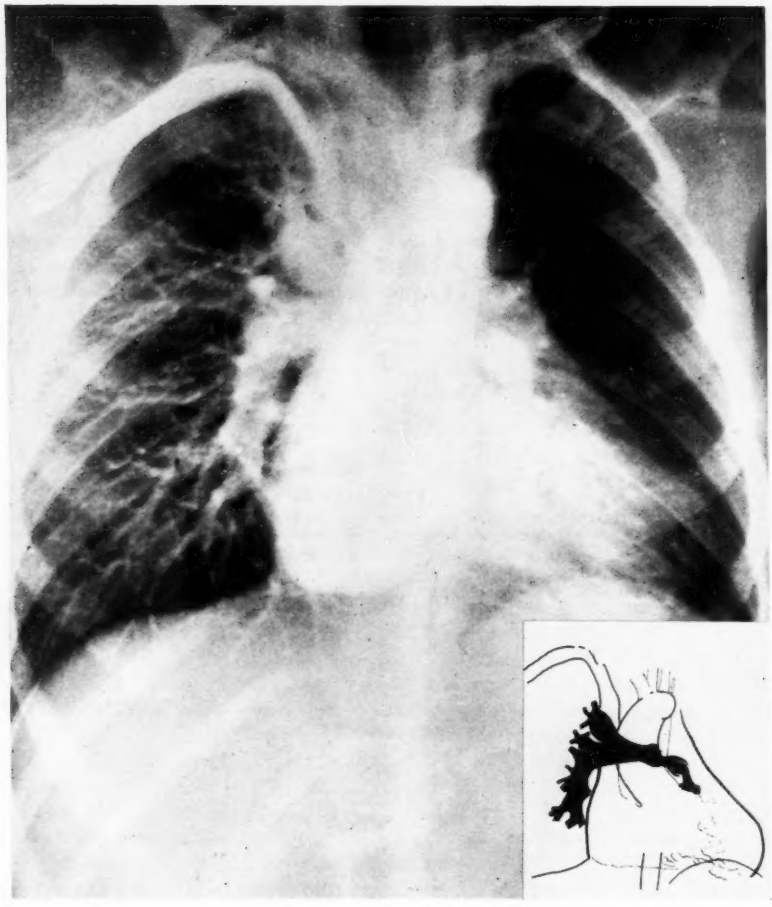

FIG. 3.—Angiocardiogram, showing absence of the left pulmonary artery associated with Fallot's tetralogy. Case 1.

Conclusion. Fallot's tetralogy with valvular and infundibular stenosis. Absence of left pulmonary artery with dilatation of the right pulmonary artery and major branches.

Case 2. This boy, aged 17 years, was investigated at Guy's Hospital and admitted to the Middlesex Hospital for operation in January, 1954. Cyanosed and clubbed since birth, with a history of frequent squatting until the age of 13 years. Severe effort intolerance, able to walk only a few yards before dyspnœa forced him to stop. Rheumatic fever when aged 9 and 11 years. Hæmoptyses when 13 years.

Mentally normal. Slight scoliosis and increased anteroposterior diameter of chest. Severe cyanosis and clubbing. Venous pressure normal. Marked arterial pulsation in neck. Pulse regular, 100 a minute, small volume. B.P. 125/85 mm. Hg. Apex beat in anterior axillary line, not remarkable in character. First sound split at apex, second sound single at base followed by an immediate diastolic murmur which occupied the whole of diastole. No systolic murmur.

Electrocardiogram: sinus rhythm with right ventricular hypertrophy of moderate degree (right axis deviation, vertical heart, deep S waves V1–6, and T negative in V1 only). Hb. 160 per cent, 23·2 g. P.C.V. 85 per cent. Chest X-ray: slight cardiac enlargement, with prominence of right ventricle; right-sided

aortic arch, rib notching confined to right side, lungs oligæmic. Angiocardiogram (poor quality films): right-sided aortic arch filling from right ventricle; no main pulmonary artery seen, but both lung roots appeared to opacify, the right more so than the left; periphery of both lung fields equally filled. Cardiac catheterization: R.V. pressure of 96/2 mm. Hg with a brachial artery pressure of 90/60; oxygen saturation of blood from R.V. 56 per cent (4 samples) and from the brachial artery 65 per cent (2 samples).

This was considered to be a case of Fallot's tetralogy with rheumatic aortic incompetence. The site

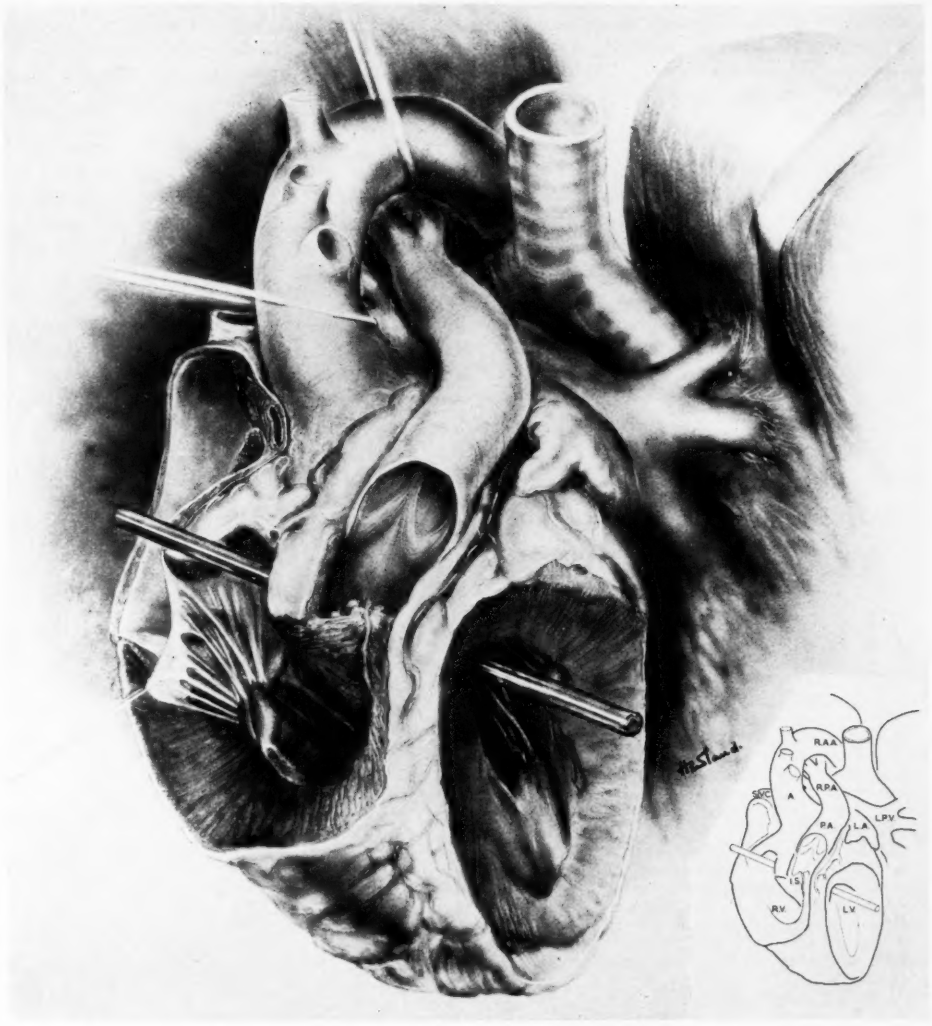

FIG. 4.—Drawing of necropsy specimen, showing absence of the left pulmonary artery associated with Fallot's tetralogy. Case 2. The rod is placed through the ventricular septal defect. S.V.C., Superior vena cava A., Aorta. R.A.A., Right aortic arch. P.A., Pulmonary artery. R.P.A., Right pulmonary artery. I.A., Left atrial appendix. L.P.V., Left pulmonary vein. R.V., Right ventricle. I.S., Infundibular stenosis. L.V. Left ventricle.

of the pulmonary stenosis was not determined. Both right and left pulmonary arteries were thought to be present, though the left lung filled less than the right.

Operation. Many highly vascular adhesions between left lung and chest wall. Very large aorta and right ventricle. Small pulmonary artery and right main branch. No evidence of left pulmonary artery. Localized infundibular stenosis palpated. Death occurred five hours after attempts to enlarge the stenosed infundibulum.

Necropsy. The cause of death was bleeding from intercostal vessels and vascular adhesions. The presence of Fallot's tetralogy was confirmed. The L.P.A. was found to be completely absent. An infundibular pulmonary stenosis which was 1·7 cm. in length admitted only a small probe. The cusps of the pulmonary valve were abnormal. The aortic cusps were thickened and thought to be incompetent, but there was no evidence of stenosis. The foramen ovale was not sealed. Both right and left ventricles were hypertrophied (Fig. 4).

Summary

Two cases of Fallot's tetralogy are described in which the left pulmonary artery was absent.

We have collected a further 19 reported cases of congenital heart disease in which the development of the bulbus cordis was abnormal and was associated with absence of the left pulmonary artery. Of these, 18 occurred with Fallot's tetralogy. No case was found where abnormal development of the bulbus cordis was associated with absence of the right pulmonary artery.

In cases where the heart was normal or the cardiac anomaly did not involve the bulbus cordis, it was nearly always the right pulmonary artery that was absent (17 out of 19 cases).

In cases of Fallot's tetralogy associated with absence of the L.P.A. an unusually high incidence of right-sided aortic arch was observed—12 out of 20 cases or 60 per cent.

An embryological explanation is postulated to explain these findings: it supports Bremer's views on the development of the pulmonary arteries in man.

We are indebted to Dr. Evan Bedford for his help with the preparation of this paper and his permission to publish Case 1. We are grateful to both Dr. Maurice Campbell and Mr. T. Holmes Sellors for permission to publish Case 2. We received much help and guidance with the embryological aspects from Professor E. W. Walls.

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PREMATURE OBLITERATION OF THE FORAMEN OVALE

BY

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Obliteration of the foramen ovale occurring during intrauterine life is a rare condition. It throws some light on the mechanism of development of endocardial fibroelastosis and also upon the factors concerned in determining the size of the aorta and of the cardiac chambers.

Case History

The patient was the second child of a mother (*aet.* 21) whose previous obstetric history was normal. Apart from two periods of rather rapid gain of weight for which no cause could be found, the pregnancy was uneventful. The child was eleven days postmature; labour was induced with an enema and lasted forty-five minutes.

The infant cried lustily but was cyanosed: the heart was clinically normal. Abnormalities were present in all four limbs. The left radius and ulna were absent and rudimentary digits were present on the skin over the distal end of the limb. Terminal phalanges were absent in the fingers of the right hand, and four toes were present on each foot with a rudimentary fifth digit on the left foot.

Cyanosis and dyspnœa became more intense and the child died three hours after birth despite the use of oxygen.

Necropsy

The body was that of a full-term male infant (weight 3430 g.). The limbs were abnormal as previously described. The lips were blue-black in colour.

On the septal wall of the right atrium a hemispherical grey-white area (10×12×4 mm. deep) with a central dimple filled in the usual site of the fossa ovalis (Fig. 1). This membrane was convex towards the right atrium; the central dimple disappeared after fixation.

There was no communication between the atria. Neither right atrium nor right ventricle were distended or hypertrophied. The tricuspid and pulmonary valves were normal. Four pulmonary veins entered a small left atrium which was slightly smaller than the left auricle, itself of normal size. The wall of the atrium was grey-white in colour. The apex of the heart and a third of its left border were formed by the right ventricle, the left ventricular chamber being a small appendage attached to the right; the thickness of the left ventricle was normal (10 mm.). The thin translucent cusps of a normal mitral valve contrasted sharply with the silvery-grey endocardial lining of the left ventricle (Fig. 2). Tiny nodular thickenings were present on the ventricular aspect of the aortic cusps. The coronary ostia were normal in position and the branches of the coronary arteries were patent. The ascending and transverse parts of the thoracic aorta were of small calibre (8 mm. circumference) and a further narrowing (5 mm. circumference and 3 mm. long) occurred immediately proximal to the junction of the aorta with a wide ductus arteriosus (20 mm. circumference) the internal lining of which was corrugated and of grey-yellow colour. The descending thoracic aorta was of normal circumference (15 mm.).

The lungs were congested and pieces from all lobes sank in water. No abnormality was found in other organs.

Microscopic Findings. A section of left ventricle showed elastic thickening of the endocardium. Dilated blood channels were seen in the subjacent myocardium; serial sections demonstrated their communication with the cavity of the left ventricle (Fig. 3). A section through the superior part of the obliterated foramen

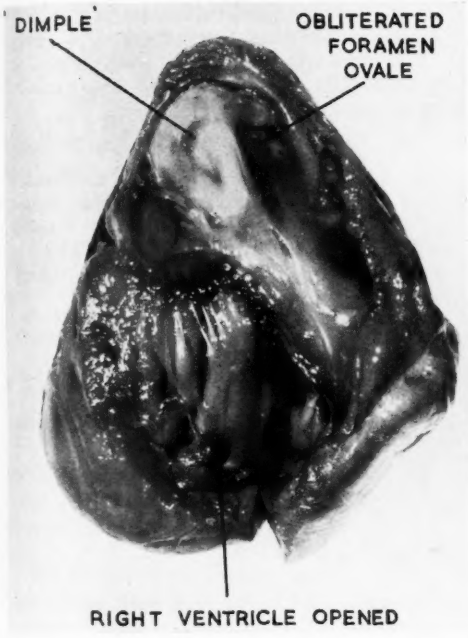

FIG. 1.—Right atrium and ventricle opened before fixation, showing dimple in obliterated foramen ovale.

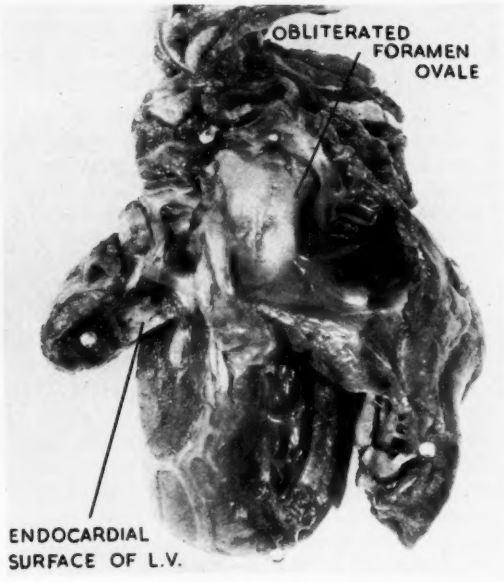

FIG. 2.—Showing the relative proportions of right and left ventricle and the thickened left ventricular endocardium.

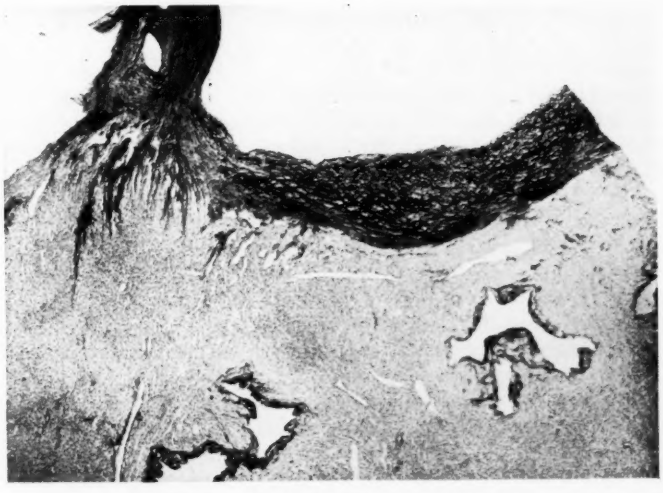

FIG. 3.—Section of left ventricle, showing elastic thickening of the endocardium and dilated subendocardial sinusoids (Weigert's elastic, ×28).

ovale showed normal endocardium on each side and in the superior part of the section a longitudinal slit lined by endothelium beneath which were strands of collagen and elastic tissue. This slit most probably represents a space between the fused septum primum and septum secundum. A thick layer of cardiac muscle, beneath the endocardium, mainly on the left side would explain, by shrinkage, the disappearance of the dimple in the obliterated foramen ovale which was present before fixation.

Compared with controls the left atrial endocardium was not thickened nor was fibroelastosis found in the right atrium or ventricle.

The only other histological abnormalities were seen in the lungs. Sections from all lobes, specifically stained for elastic tissue showed a slight but significant increase of elastic in the intima and media of arterioles as compared with controls. Many macrophages in alveoli contained a black pigment some of which stained blue with Perls' and with Turnbull's methods. Repeated washings of the sections with a saturated solution of picric acid in 85 per cent alcohol failed to remove the remainder of the pigment which was hence unlikely to be derived from formalin.

Discussion

Only eight reported cases that can be considered to be examples of premature obliteration of the foramen ovale upon the evidence provided have been found.

The first, in a child " of a livid colour " living 36 hours, is that of Vieussens (1715) (quoted by Corvisart, 1813). " The lungs were much swollen and their vessels gorged with blood; the right ventricle and the pulmonary artery were very much dilated; and no trace could be found of the foramen ovale." No further details of the heart are given. An example of this condition in a child, one day old, described by Morgagni (1761) has escaped mention in previous reports. However, as in the last case, information is scanty concerning the rest of the heart.

Smith (1846) contributed a specimen of a heart showing premature obliteration of the foramen ovale to the museum of Guy's Hospital; unfortunately it is no longer available. The heart was taken from a child which was cyanosed within five minutes after the beginning of respiration, deeply cyanosed and comatose in eleven hours, and dead in twenty-one hours. " The fossa ovalis . . . entirely closed by a strong reticulated membrane firmly attached to its annulus and forming a pouch projecting towards the left side. . . . The left ventricle was almost obliterated . . . lined by a very dense smooth membrane." Bulging of the obliterated foramen ovale towards the left atrium would agree with the expected raised pressure on the right side of the heart. In the present case the obliterated foramen bulged to the right; this may have been due to post-mortem contraction of the thicker mass of cardiac muscle on the left side of the atrial septum compared with that on the right side.

A case is described by Vernon (1856) of absent ductus arteriosus, overriding aorta, small left ventricle, and a ventricular septal defect together with a closed foramen ovale in a child cyanosed at birth and living four hours. However, to say that the foramen ovale is closed, not obliterated, in a newborn child is to state a normal finding and it is doubtful if this case can be included as an example of obliteration of the foramen ovale. Post-mortem examinations of stillborn and neonatal infants reveal in most cases a closed foramen ovale but usually a fine probe can be made to pass from right to left atrium through a postero-superior valvular slit (Fig. 4). This slit can be made visible, in some cases, by altering the position of the heart while looking into the opened right atrium. Johnson (1952) quotes six cases of closed foramen ovale in association with fibroelastosis from a paper by Craig (1949); this latter author states that the foramen ovale was closed but does not mention if a valve was present. It is probable that the foramen was valvular in these cases as the author does not emphasize or comment upon the " closed " foramen ovale. Osler (1880) and Brenner (1939) both regard a valvular foramen ovale at birth as being prematurely closed: the detailed studies of Patten (1938) show that such a concept is not now tenable. The case described by Osler and that of Tait (1875) were probably examples of hydrops fœtalis though insufficient detail is provided to be certain. Generalized œdema at birth was a feature of both of these cases and Lehman (1927) considered that this formed one of the clinical variants of premature closure of the foramen ovale; the other two varieties being cases with progressive cyanosis leading to death

and those in which the abnormality was associated with multiple cardiac defects. There are no grounds for including those cases with valvular foramen ovale showing generalized œdema at birth as examples of obliteration of the foramen ovale.

The clinical picture in all reported cases of obliteration of the foramen ovale, without septal defects or overriding great vessels, was progressive cyanosis leading to death, and in these cases the left ventricle showed fibroelastosis as judged by microscopic appearances in all except that of Smith

FIG. 4.—Heart of a newborn child (*aet.* 10 hours); right atrium opened in situ to show closed foramen ovale.

(1846); in this case the macroscopic appearances suggested fibroelastosis. The constant presence of ventricular fibroelastosis in those cases in which adequately oxygenated blood is practically excluded from the left ventricle supports the view of Johnson (1952) that anoxia of the ventricular endocardium plays a part in the production of fibroelastosis. This concept is strengthened by the fact that the coronary circulation is developed progressively throughout embryonic life; the myocardial blood supply being first derived from sinusoids communicating with the lumen of the ventricle. It is probable that obliteration of the foramen ovale early in intrauterine life would lead to severe endocardial anoxia which may be responsible for the fibroelastic thickening of the ventricle. The small size of the atrial, ventricular, and aortic cavities may be explained by the diminished blood flow through them. In the present case the aorta was hypoplastic in its ascending and part of its transverse portion and showed an area of coarctation proximal to its junction with the ductus arteriosus. A more severe degree of aortic narrowing producing atresia, in a case with obliteration of the foramen ovale and atresia of the mitral orifice, is reported by Bellet and Gouley (1932): here also the left ventricle was small and showed fibroelastosis. A curious observation is the normal and sometimes increased thickness of the wall of the left ventricle in these cases despite the diminished flow through the chamber, in utero.

The degree of fibroelastic involvement of the left atrium is difficult to assess as the amount of subendocardial elastic and collagen varies throughout the atrial endocardium. In control cases the

amount of elastic is greatest in the posterior parts of the left atrium and hence the site from which a section is taken must be clearly stated before an opinion is expressed as to the degree of elastic thickening of the endocardium. Several authors (Johnson, 1952; Bellet and Gouley, 1932; and Edwards and Du Shane, 1950) state that fibroelastosis was present in the left atria in their cases. In the present case the macroscopic appearances of the atrium were suggestive of fibroelastosis but comparison of sections with controls showed very little difference in the amount of elastic present.

The membrane obliterating the foramen ovale in the case here reported consisted almost entirely of muscle. This suggests that the obliteration was due to abnormal development rather than to inflammatory thickening; the former view is supported by Patten (1938) who postulates failure of development of the septum secundum as the cause. Against this view is the slit found in the present case in sections through the obliterated foramen ovale that may represent a space between septum primum and septum secundum. A few strands of muscle are found in sections through the foramen ovale of the newborn; however, they undoubtedly undergo hypertrophy in the obliterated foramen ovale as seen in the present case due to the increased pressure in the right atrium.

The course of the circulation in utero in this infant was probably abnormal from about the eighth week—the time of completion of development of the atrial septum. Most of the blood received by the right atrium would probably pass through the ductus arteriosus to the aorta. Despite this the pulmonary blood flow was probably greater than is normal in fœtal life and this may account for the slight degree of intimal hypertrophy seen in the pulmonary blood vessels. The source of the alveolar pigment is obscure.

The progressive cyanosis at birth may be explained by shrinkage of the ductus producing an increased blood flow through the small left side of the heart; not only was the volume of blood too great for the small chambers but also the aortic resistance would be high and this no doubt led to acute cardiac failure.

Summary

The ninth case of premature obliteration of the foramen ovale is described. Previously reported cases are reviewed and discussed.

The constant finding of left ventricular fibroelastosis in these cases supports the view that anoxia plays a part in its production.

The valvular nature of the foramen ovale at birth is emphasized.

I am grateful to Dr. D. Gairdner for permission to publish this case, to Dr. A. M. Barrett for his constant encouragement and advice, to Dr. B. Towers for his patience in explaining the embryological details, and to Dr. Keith Simpson for information concerning the specimen described by Smith (1846). I wish to thank Miss S. Westoby and Mr. S. Patman for the photographs.

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ABERRANT BEATS OF WOLFF-PARKINSON-WHITE CONFIGURATION IN ARTERIOSCLEROTIC HEART DISEASE

BY

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Evidence has been presented by Prinzmetal *et al.* (1952) and Borduas *et al.* (1955) that electrocardiographic beats characterized by short P–R and long QRS intervals may occur in the absence of an accessory pathway by-passing the A-V node. In animal experiments, Prinzmetal observed beats of WPW type after repeated electrical stimulation of the A-V node, and noted in these same animals the spontaneous occurrence of various supraventricular tachycardias. Several arteriosclerotic patients studied by Prinzmetal demonstrated similar electrocardiographic phenomena, and at necropsy were found to have fibrotic disease of the A-V node and no accessory conduction system. These clinical and experimental observations indicate that WPW beats may occur on an acquired basis, secondary to nodal disease.

In other experiments, Prinzmetal induced beats of WPW type in dogs after repeated ventricular stimulation with the A-V node intact. These observations harmonize with those of Kossman *et al.* (1950) who recorded such beats during cardiac catheterization when the catheter was in direct contact with the endocardial surface. Similar complexes have been observed by Prinzmetal during the course of acute myocardial infarction, frequently in association with ventricular premature beats and ventricular arrhythmias.

On the basis of his extensive studies, including high-speed cinematographic techniques, Prinzmetal has deduced that accelerated conduction through part of the A-V node is responsible for aberrant complexes. He believes this to be true both in instances of nodal disease (" nodal " accelerated conduction) and ventricular irritability (" ventricular " accelerated conduction). In this latter type, the accelerated conduction through the A-V node may be on a reflex basis.

Five instances of WPW aberration have been seen during the past two years in patients with arteriosclerotic heart disease. Of these, four are considered to be of acquired type, and only one an example of classical, congenital, Wolff-Parkinson-White syndrome (1954).

Case Reports

Case 1. A 54-year-old man, who had had effort angina for one year, was admitted because of severe chest pain, of 48 hours' duration. The clinical course and serial electrocardiograms were characteristic of posterior wall infarction.

Fig. 1A demonstrates numerous premature ventricular beats. In Fig. 1B, in addition, beats of WPW type may be seen in leads II, AVR, and V6. Fig. 1C shows a run of ventricular tachycardia (Lead I).

On three separate occasions, the oral administration of procaine amide or quinidine abolished the premature ventricular beats, the beats of WPW type, and the short runs of ventricular tachycardia.

This case represents the " ventricular " type of acquired WPW aberration. In the experience of Prinzmetal (1952) " ventricular " WPW is usually associated with anterior infarction, and " nodal " WPW with posterior infarcts. Perhaps with increasing experience additional examples

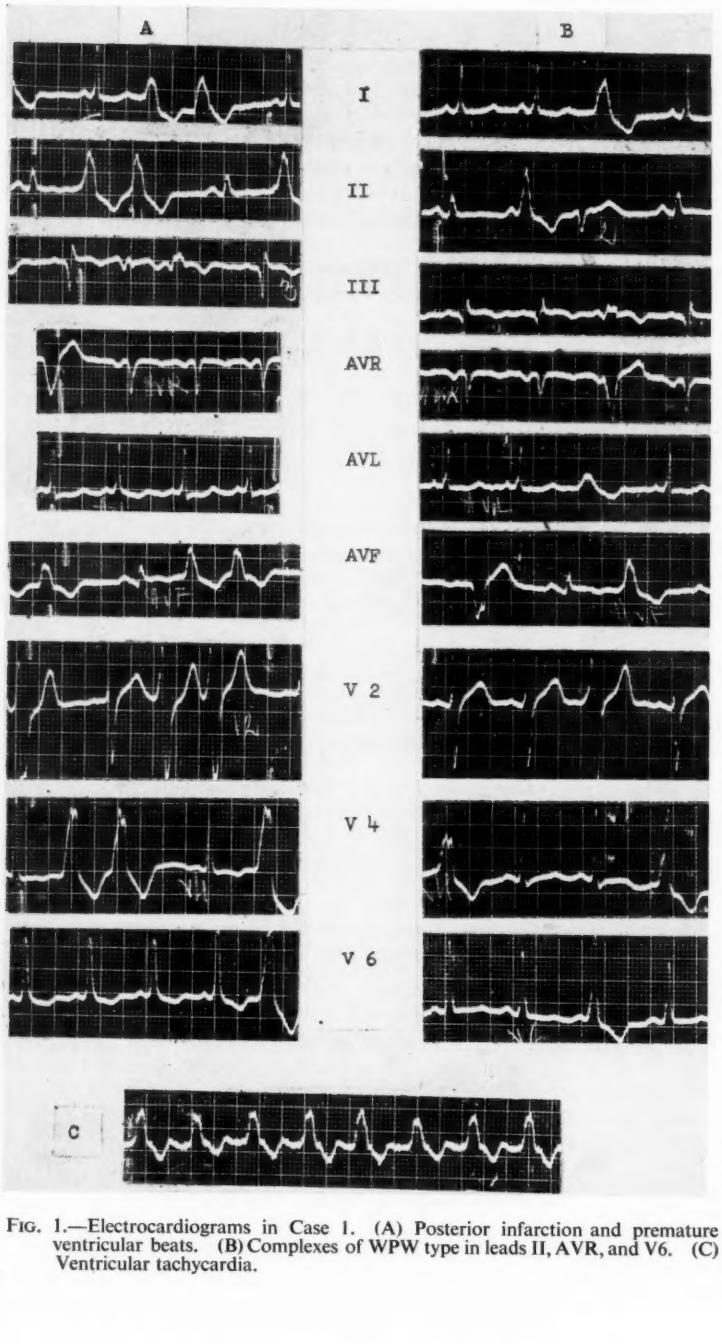

FIG. 1.—Electrocardiograms in Case 1. (A) Posterior infarction and premature ventricular beats. (B) Complexes of WPW type in leads II, AVR, and V6. (C) Ventricular tachycardia.

of the " ventricular " type in posterior infarcts will be seen. There can be no doubt of the efficacy of procaine amide and quinidine in suppressing not only the arrhythmia and premature ventricular beats, but the aberrant conduction as well.

Case 2. A hypertensive woman aged 52 was admitted because of dyspnœa and substernal pressure, both on effort. For three days she had noted paroxysmal nocturnal wheezing and orthopnœa. Previous blood pressures had averaged 190/120. The blood pressure on admission was 140/90; at the apex gallop rhythm and friction rub were audible. Basal moist râles were present. Treatment included oxygen, morphine, digitalis, and heparin. The course was favourable, with gradual recovery over a four-week period.

Fig. 2A and 2B show serial T changes as well as prominent Q in lead III. Localization of the infarct was not certain, but acute anterior disease and old posterior disease seemed likely. On one occasion only, WPW beats were seen alternating with normal beats. This is shown in Fig. 2C.

Case 3. A 58-year-old man was admitted because of progressive effort angina. The diagnosis of coronary insufficiency had been made four months before admission. His need for nitroglycerine had increased from three or four daily to almost hourly. X-ray studies demonstrated left ventricular enlargement. Physical examination, white counts, and sedimentation rates remained normal during three weeks in hospital.

The electrocardiograms (Fig. 3A and 3B) show serial S–T and T changes, as well as Q waves in leads I and AVL. Anterolateral disease was considered definite, but actual acute infarction could not be diagnosed with certainty. Lead I of Fig. 3B shows beats of WPW type alternating with normally conducted beats.

Comment on Cases 2 and 3. These two cases demonstrate beats of WPW type alternating with normal beats. Because of the absence of premature ventricular complexes, the aberrant conduction is probably of the " nodal " variety. No arrhythmia occurred in either patient. Quinidine or procaine amide were not given to prevent possible arrhythmia, as at the time these patients were treated the full significance of the aberrant beats was not appreciated. Similar patients observed now would in all likelihood be given a nodal depressant drug as prophylaxis against arrhythmia.

Case 4. A 62-year-old man entered the clinic because of fatigue, dyspnœa, and intermittent claudication. Pertinent findings included a blood pressure of 190/80, a regular bradycardia of 50 beats a minute, and sclerotic retinal and brachial vessels. Posterior tibial and dorsalis pedis pulses were absent. A loud, long apical systolic murmur was audible. X-rays showed that the heart was not enlarged.

The electrocardiogram (Fig. 4) shows in the frontal plane leads, a normal sinus rhythm, short P–R and wide QRS intervals. A spontaneous change in mechanism then occurred, as the praecordial leads reveal a 2–1 A-V block, with each conducted beat having the WPW configuration.

The coexistence of A-V block and WPW aberration accords well with Prinzmetal's view that a diseased A-V node may at times conduct more slowly than normal, and at other times more rapidly. He has observed two such cases which ultimately came to autopsy; fibrotic nodal disease was found in each case. Levine and Burge (1948) reported a very similar case. Their patient had acute myocardial infarction with complete heart block. Occasional atrial impulses were conducted, however, and all of these were characterized by short P–R and wide QRS complexes of the WPW type. Autopsy disclosed an accessory right lateral bundle, which apparently became functional after destruction of the A-V node by disease. Thus, when WPW aberration and heart block co-exist, accessory conduction tissue as well as accelerated nodal conduction must be considered.

Case 5. A 30-year-old man was in hospital because of severe crushing substernal pain of one hour's duration. The pain radiated to the neck and was accompanied by severe dyspnœa. The past history included repeated, frequent bouts of palpitation. A cardiac study at the age of 16 had disclosed Wolff-Parkinson-White syndrome. The present hospital course was favourable, with discharge in three weeks. Serial studies of white count and sedimentation rate were equivocal.

Fig. 5A is the electrocardiogram taken at the age of 16 and showing short P–R and wide QRS intervals. Fig. 5B, taken on admission, is not significantly different. In Fig. 5C, however, a spontaneous reversion to normal conduction occurs in many beats, disclosing markedly abnormal T waves in leads II, III, and V6.

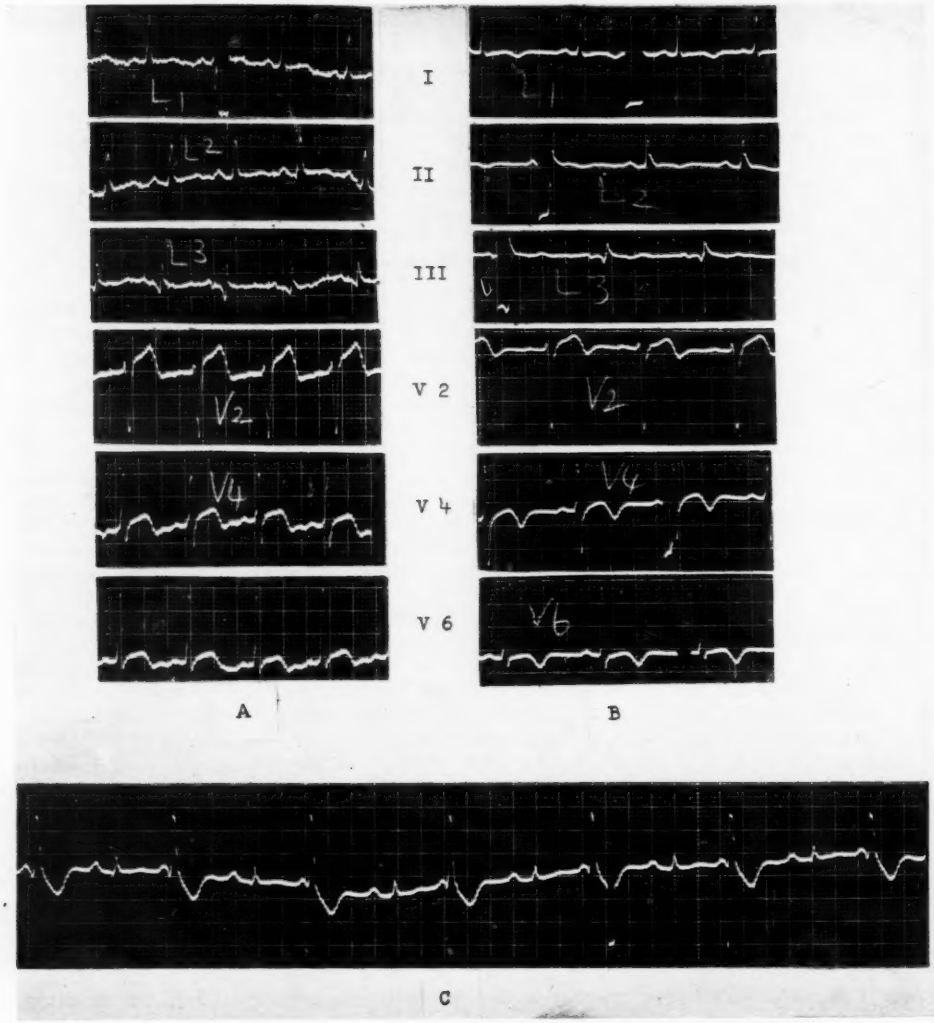

FIG. 2.—Electrocardiograms in Case 2. (A) and (B) Serial S–T and T changes. (C) Beats of WPW type alternating with normally conducted beats.

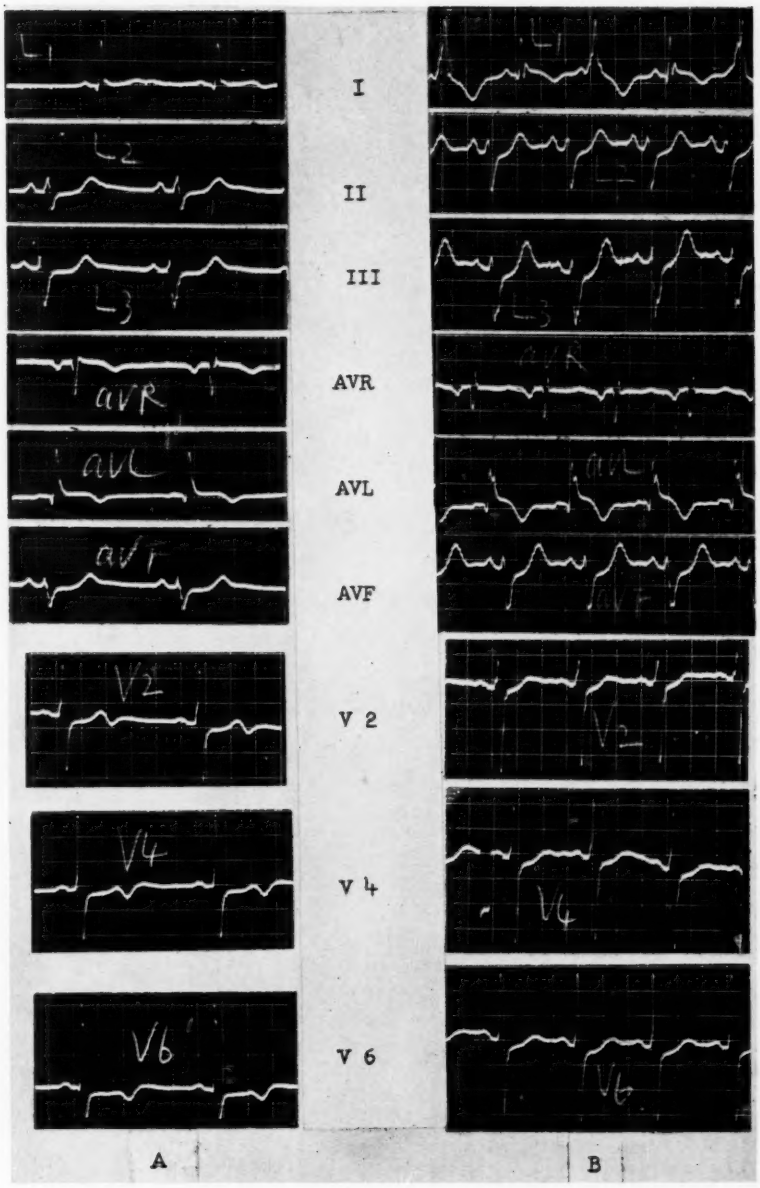

FIG. 3.—Electrocardiograms in Case 3. Serial S–T and T changes. Alternating beats of WPW type in lead I (B).

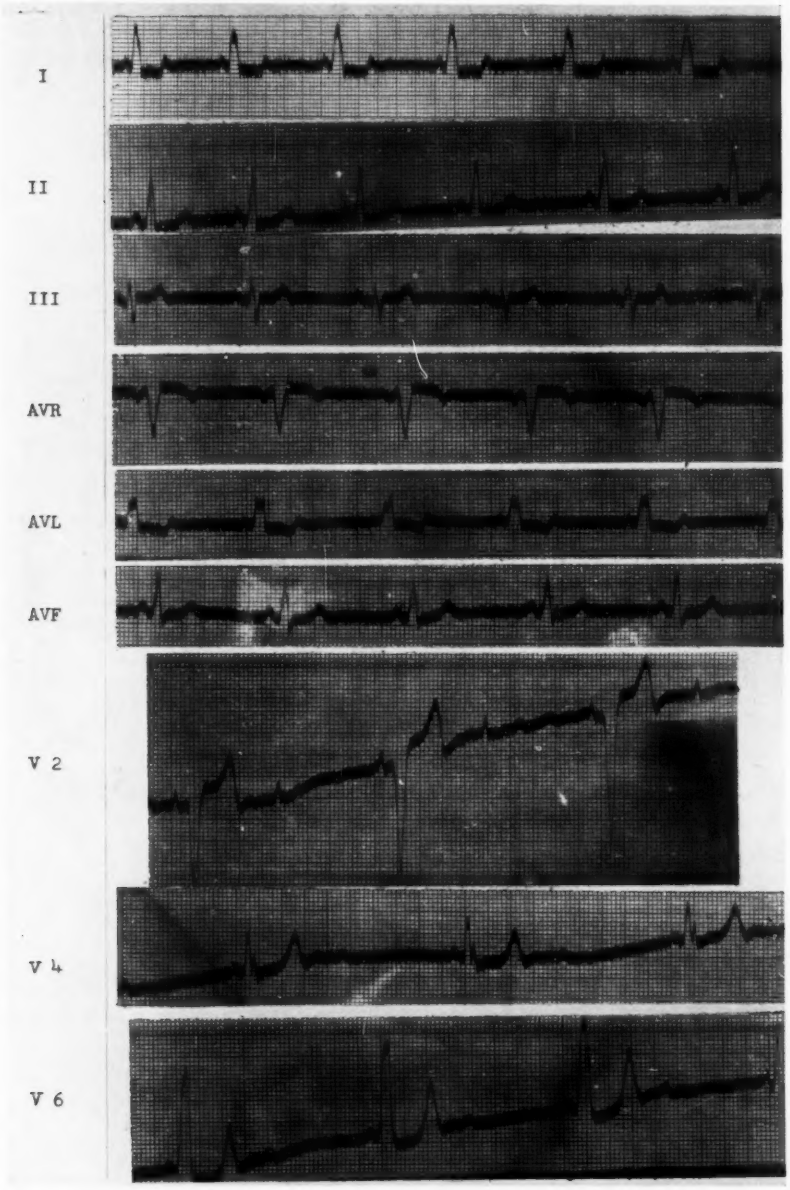

FIG. 4.—Electrocardiogram in Case 4. Frontal plane leads show WPW aberration. V2, V4, V6 show in addition 2:1 atrioventricular block.

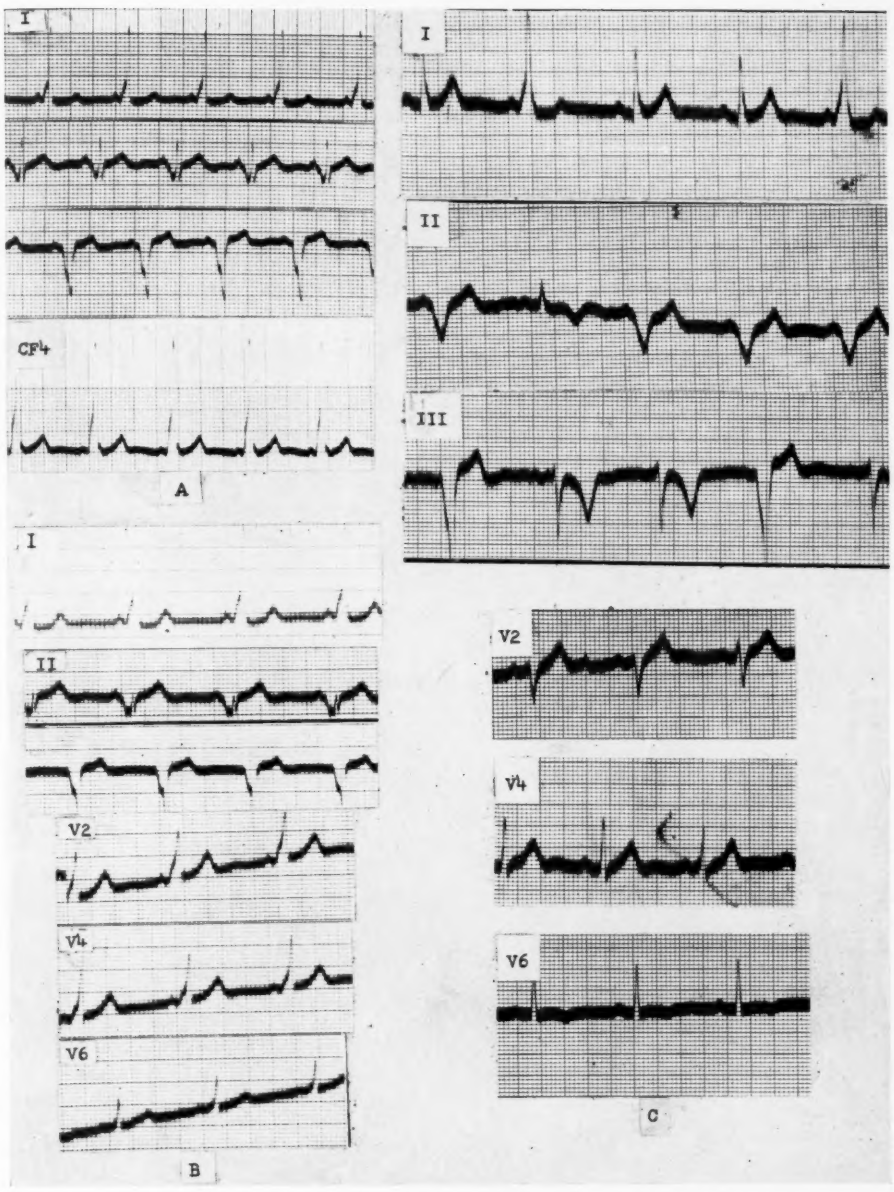

FIG. 5.—Electrocardiograms in Case 5. (A) Electrocardiogram at age 16, showing WPW aberration. (B) Electrocardiogram on admission at age 30 for chest pain. (C) Abnormal T waves in leads II, III, and V6 recorded with spontaneous reversion to normal conduction.

This case illustrates coronary insufficiency and perhaps myocardial infarction in a young man with classic WPW syndrome. In this instance, as in the cases of Zoll and Sacks (1945) and Goldbloom and Dumanis (1946), the aberrant conduction obscured the diagnosis.

Discussion

These five instances of WPW aberration in the course of arteriosclerotic heart disease were seen during a two-year period at three active hospitals. The incidence, therefore, may be considered low. The proportion between acquired (4 cases) and congenital (1 case) varieties is, nevertheless, striking.

The recognition of these complexes is important as they may precede serious arrhythmias—supraventricular in the " nodal " type and ventricular in the " ventricular " type. In the present series quinidine and procaine amide were used in one case, with good effect. Even though these aberrant beats are not always followed by arrhythmia, it would seem reasonable to administer nodal depressant drugs as a prophylactic measure if no contra-indication, such as heart block, exists.

Summary

Five examples of electrocardiographic aberration of WPW type occurring in the course of arteriosclerotic heart disease are presented.

Of the five, four are considered to be acquired and one congenital.

These aberrant beats may precede arrhythmias, and, therefore, suggest the use of prophylactic nodal depressant drugs.

The authors wish to thank Col. Ryle A. Radke, Chief, Medical Service, Tokyo Army Hospital, for permission to include Cases 2 and 3, and Dr. Orgain of Duke Hospital for the electrocardiograms in Case 5.

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SUPERNUMERARY CHAMBERS TO THE LEFT HEART

BY

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Unique abnormalities were found in the hearts of two patients who recently came to necropsy. A supernumerary left atrium was present in each and communicated with the left ventricle by means of an ostium distinct from the mitral valve. In one of these hearts there was an additional miniature ventricle on the left, and in the other there was possibly a rudimentary extra ventricle. The clinical findings in one of these patients were distinctive enough to have made clinical diagnosis possible. In each instance the anomaly contributed directly to the patient's cardiac difficulties.

Case Reports

Case 1. Accessory left-sided two-chambered heart (Bantu girl, aged 5 years).

Shortness of breath had been noticed since birth, but the child had apparently developed normally. Three weeks before admission she began to cough spasmodically, becoming very dyspnœic and blue, and occasionally vomiting.

On examination, abnormalities were confined to the cardiovascular system and the lungs. She was short of breath at rest, but there was no cyanosis, no abnormal venous pulsation, no distension of the neck veins, nor any other signs of failure. Numerous moist crepitations were scattered through both lung fields. The blood pressure was 100/68 mm. Hg and the pulse rate 130 a minute. The heart was enlarged and the apex beat had a left ventricular quality impulse, maximal in the anterior axillary line. A grade III systolic murmur was conducted round toward the axilla to the left. A blowing diastolic murmur, quite unlike the rumble of mitral stenosis, was localized to the mitral area. The first mitral sound was not accentuated. There were no murmurs at the base of the heart and the second pulmonic sound was normal.

The heart was enlarged and there was much prominence in the region of the left auricular appendage and in the posterior-anterior view (Fig. 1). This shadow could not be separated from the rest of the atrial shadow on rotating into the oblique positions, and appeared to be attached to the left atrial appendage and pulsated actively and in time with the pulmonary artery and aorta. In oblique views the cardiac enlargement appeared to be due to enlargement of the left ventricle. The barium-filled œsophagus showed no left atrial enlargement.

The electrocardiogram showed sinus rhythm with a P–R interval of 0·12 sec. It showed a normal axis and a vertical heart position. The S wave of 20 mm. in V1 with a predominant R wave of 7 mm. in V6 and slight S–T depression in V4, V5, and V6 were evidence of left ventricular hypertrophy. There was some T inversion in V1–V3 but in a child of this age this was thought to be normal.

The urine contained a trace of albumin. The hæmoglobin was 80 per cent (11·9 g. per 100 ml.); the red blood cells, 4,620,000, per c.mm.; and the white blood cells, 27,000 per c.mm. with a neutrophilic predominance. The Kolmer and Khan tests were negative.

During the patient's stay in hospital she had a temperature of 99°–101° F. She was treated with antibiotics and digitalized. There was no improvement, however, and she gradually declined and died three weeks after admission.

Necropsy findings. There was no dependent œdema or transudate within the serous cavities. A small caseous, partially calcified lymph node occupied the left lung hilus. No Ghon focus or other abnormality was discovered in the lungs. All organs except the heart were normal and there were no signs of passive venous congestion.

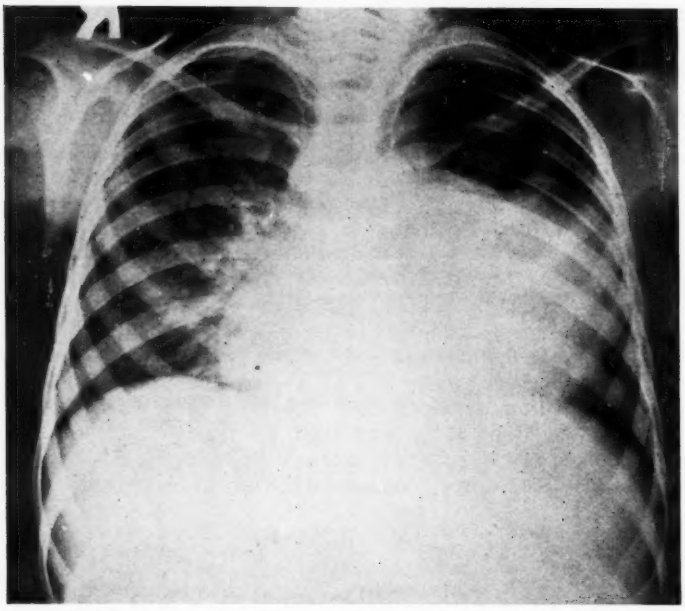

FIG. 1.—Posterior-anterior film of chest, illustrating prominence in region of the left atrial appendage. Case 1.

The heart weighed 170 g. (normal 90 g.). This normal weight and the values given for thicknesses of cardiac chambers, as well as normal measurements of valvular circumferences have been taken from the tables set out by Gould (1953). The most striking feature of this heart was a large sac lying to the left of the left atrium (Fig. 2). The pericardium was adherent over the entire heart, including the sac.

The right atrium was normal, its wall averaging 1 mm. in thickness. The coronary sinus and great veins entered normally. The tricuspid valve was properly formed and was attached by normal chordæ to anterior, posterior and conus papillary muscles.

Both conus and body of the right ventricle had undergone hypertrophy. The mean thickness was 3 mm., which equalled that of the normal adult ventricle (2–3 mm.). Dilatation had taken place because the right A-V ring was 9 cm. in circumference, a figure close to those recorded for adult women. The pulmonic valve was normal and measured 4·5 cm. in circumference. Immediately beyond it the pulmonary trunk was 4·8 cm. in circumference. Neither the trunk nor its main branches were dilated or involved by arteriosclerosis.

The left atrium was 1–2 mm. thick (normal 1–2 mm.). Its wall was united with the adjacent sac wall by adhesions only. Pulmonary veins of normal calibre entered at the usual sites. The mitral valve, its chordæ, and their attachments to papillary muscles were normal, except that the mitral ring at its lateral edge was not united with myocardium for a distance of 1 cm. Immediately lateral to this free part, but medial to the left ventricular wall, was situated an oval ringed aperture, 3 cm. in circumference, which gave access to the sac (Fig. 4). The left ventricular wall was hypertrophied, measuring 7 mm. (normal adult 8–10 mm.) and dilated, since the circumference of the mitral ring was 9 cm. equalling that for adult women. The circumference of the aortic valve was 4·5 cm., and that of aorta itself immediately above 5·5 cm. The aortic valve and aorta were normal, and the ductus arteriosus had been obliterated.

The sac (Fig. 2 and 3) was bilocular and consisted of a large, thin-walled upper compartment and a small, thick-walled lower compartment. *The upper compartment* was 8 cm. long, 6 cm. wide and 6 cm. from front to back. Corresponding figures for the lower compartment were 3, 3, and 4 cm. These compartments were marked off from one another on the outside and in front by the A-V sulcus of the heart.

FIG. 2.—The four-chambered heart and the left-sided two-chambered accessory heart. The anterior walls of the sac and the ventricles have been cut away. Upper and lower compartments of the two-chambered heart are delimited by the atrio-ventricular sulcus of the four-chambered organ. (Stitches in the posterior sac wall close the site where tissue was taken for microscopical examination.) Case 1.

The upper compartment was thin, 1 mm. in its upper two-thirds, but elsewhere it measured 2 mm. Medially and posteriorly two pockets occupied by patches of fibrinous deposit were present. The endocardium was everywhere dull and opaque. This compartment neither received nor gave off any vessels. It communicated inferiorly with the lower compartment by a circular orifice possessing a smooth, firm edge (Fig. 2). This orifice was 4·3 cm. in circumference and was situated at the level of the A-V sulcus. *The lower compartment* was pyriform in shape, was 5 mm. thick and walled by myocardium. Inside it three thick cones of cardiac muscle passed medially from its anterior, lateral and posterior walls. Inferiorly, this lower compartment communicated with the left ventricle by means of an oval orifice 4·3 cm. in circumference (Fig. 3). Its medial half was formed by the free part of the mitral ring, its lateral half by tapering ring tissue that blended with locally thickened ventricular endocardium.

The origin and distribution of the coronary arteries were normal. The circumflex branch of the left

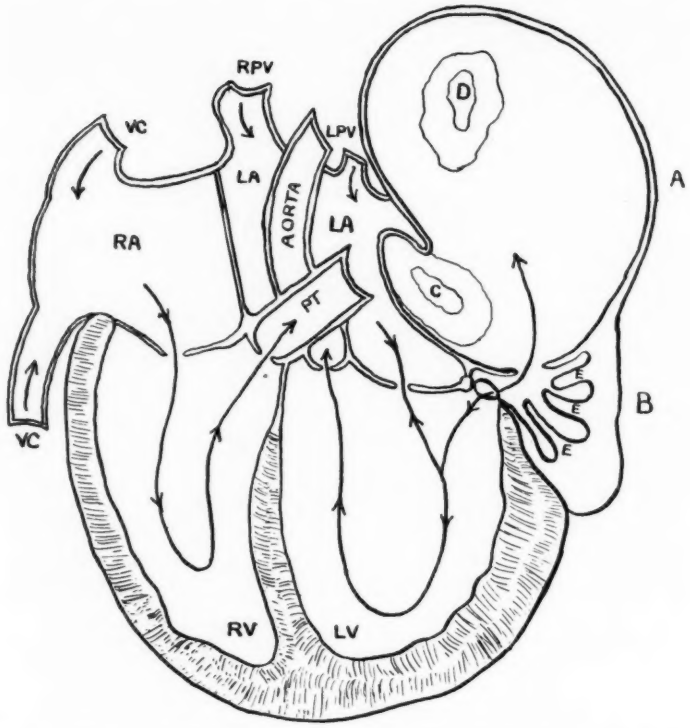

FIG. 3.—Diagram to illustrate the relationship between the two hearts. A, upper compartment, and B, lower compartment of the accessory heart. C and D are pockets coated by fibrin deposits within the upper compartment. E are trabeculæ carnæ of the lower compartment. (For the sake of simplicity the upper compartment has not been drawn as a structure separate from the left atrium.) Case 1.

coronary was the chief source of arterial blood for both compartments. Venous drainage was of normal pattern, the sac walls emptying by small radicles into the coronary sinus.

Microscopically, the left atrial endocardium was slightly thickened by fibrous connective tissue. Thin strands of cardiac muscle embedded in dense collagen formed the wall of the upper compartment of the sac which was lined by fibrosed endocardium and, in places, by organizing fibrin as well. The lower compartment consisted of normal myocardium with an outer investment of fibrosed epicardium. Small arteries within the sac wall were narrowed by endarteritis fibrosa, but in the heart itself the coronary arteries were normal. The lungs were congested only in those places where early bronchopneumonia had developed; alveolar spaces in these pneumonic areas, but not elsewhere, contained hæmosiderin laden macrophages. The alveolar walls themselves were normal. Intra-pulmonary arteries of 0·1 to 1·0 mm. external diameter were mildly involved by endarteritis fibrosa. Neither these muscular arteries nor elastic arteries of external diameter greater than 1·0 mm. were atheromatous or hypertrophied. The pulmonary veins were normal. Precapillary vessels (which are large calibre endothelial tubes resting on an elastic lamina of diminishing completeness depending upon size) were involved by transformation of the endothelium into collagen or a substance reacting only pale pink to van Gieson's stain. It was thought unlikely that these precapillary changes had of themselves been sufficient, by causing obstruction, to have produced right ventricular hypertrophy. Though spleen and kidneys were congested, this might as well have been due to active hyperæmia from the bronchopneumonia as to right heart failure.

Case 2. Bipartite left atrium consisting of right and left compartments and rudimentary left ventricular tissue (Bantu man, aged 26 years).

This patient worked as a despatch clerk in a store and was apparently quite well until three months before admission. He then began to complain of shortness of breath which appeared episodically both night and day and increased in severity and persistence so that he was soon unable to walk even a few steps. During this time he noticed swelling of the legs and abdominal distension. For one month he had coughed continuously. There were no other significant features in this patient's history, apart from the belief that he had had rheumatic fever at the age of 15 years.

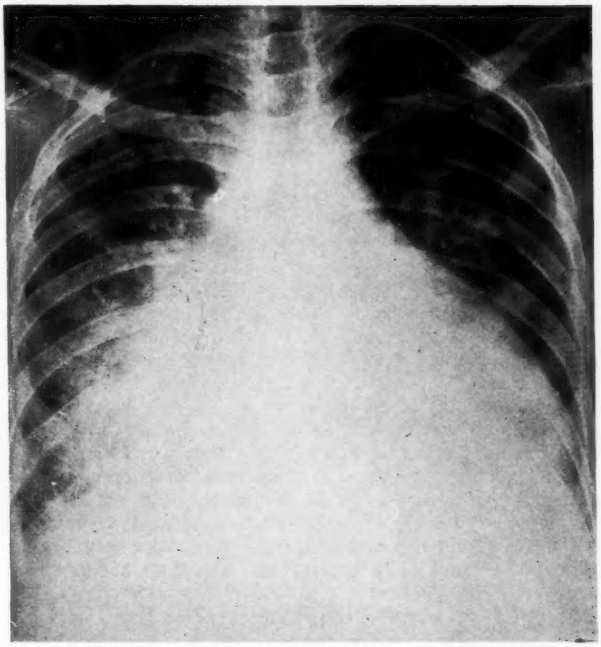

FIG. 4.—Posterior-anterior film of chest, illustrating generalized cardiac enlargement and pulmonary congestion. Case 2.

On examination he was acutely ill and orthopnœic. There was œdema of the whole body, especially the legs, and the abdomen was distended with free fluid. The heart rate was 110 a minute. The blood pressure was 130/100 mm. Hg and the extremities felt cold. The heart had a diffuse impulse maximal outside the mid-clavicular line. A systolic thrill was palpable and a harsh, systolic murmur was heard over the mitral area, conducted well round to the axilla. A late diastolic murmur with a crescendo quality was heard at the mitral area, and a third heart sound at the apex. The second pulmonic sound was accentuated.

There was generalized cardiac enlargement (Fig. 4) which appeared in the oblique views to involve both left and right ventricles. There was no evidence of left atrial enlargement. Both lung fields were much congested. The electrocardiogram (Fig. 5) showed a vertical heart position with right axis deviation. The T waves were negative in leads V3–V6. These findings were attributed to left ventricular hypertrophy.

The urine showed no abnormalities. The hæmoglobin was 90 per cent (13·4 g. per 100 ml.). The white blood cells were normal with a neutrophilic preponderance. The blood urea was 61 mg. per 100 ml. Serological tests for syphilis were negative.

The patient received intensive treatment with digitalis and diuretics, but his condition deteriorated and he died in congestive cardiac failure after six weeks in hospital.

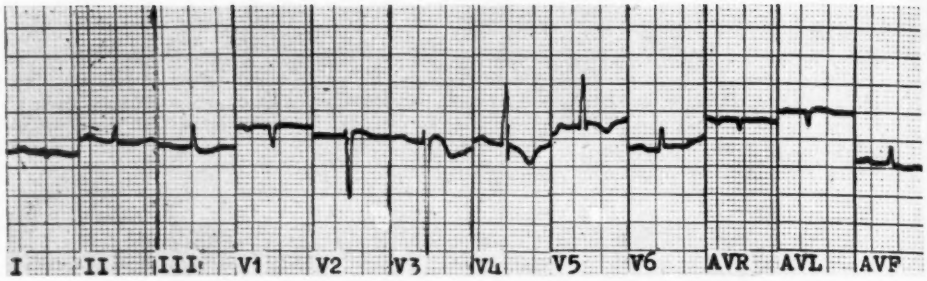

FIG. 5.—Electrocardiogram, showing the features that were interpreted as left ventricular hypertrophy. Case 2.

Necropsy findings. Severe dependent œdema, ascites (3 litres), bilateral hydrothorax (1 litre in each pleural cavity), and hydropericardium (500 ml.). The liver was passively congested and transected by a few coarse bands of fibrous tissue. A number of old infarcts were present in the kidneys. The lungs and abdominal viscera were passively congested.

The heart weighed 470 g. (normal, 312 g.). Its most arresting feature was a large sac situated beside the left atrium (Fig. 6). The sac turned out to be a dilated left compartment of the left atrium, this chamber having been partitioned into two by an incomplete, vertically directed septum.

The right atrium was dilated, its wall measuring 2 mm. in thickness (normal, 1–2 mm.). The coronary sinus and great veins entered the right atrium normally. The right atrial appendage was free from antemortem thrombus and the foramen ovale was closed. The tricuspid valve, 15 cm. in circumference (normal, 12 cm.) was intact and attached by normal chordæ to anterior and posterior papillary muscles and directly to the crista supra-ventricularis, the conus papillary muscle not having developed. A well-marked moderator band was present.

The right ventricle was greatly hypertrophied and dilated, its wall measuring 6 mm. in mean thickness (normal, 2–3 mm.). The pulmonary valve was 8 cm. in circumference (normal, 8·5 cm.) and free from pathological change. The right ventricular endocardium was not thickened. Immediately beyond the valve, the pulmonary arterial trunk was 8·5 cm. in circumference (normal, 7–9 cm., Parkinson, cited by Brenner, 1935); its extrapulmonary branches were not obviously dilated. A small, fibrous intimal plaque, 1 cm. in diameter, was found in the anterior wall of the trunk 3 cm. above the pulmonary valve. This plaque was regarded as a jet lesion. Elsewhere both trunk and its extrapulmonary branches were free from arteriosclerosis.

The right compartment of the left atrium was dilated and measured 3 mm. in thickness (normal, 1–2 mm.). Its appendage resembled a small, elongated aneurysm, 4 cm. long, which communicated with the parent chamber by a circular orifice only a little less in size than its own circumference, which was 8·5 cm. The pulmonary veins were dilated and entered the right compartment of the left atrium normally. This chamber was separated from the sac to its left (left compartment) by a vertical septum provided with an oval aperture. This septum showed no trace of either a fossa ovalis or of a valvula foraminis ovalis. The endocardium of the right compartment of the left atrium was not thickened except on its posterior wall. The right compartment opened by means of a mitral valve into an hypertrophied, dilated left ventricle, 12 mm. thick (normal, 8–10 mm.). The interventricular septum was intact.

The cusps of the mitral valve, consisting of normally formed anterior and posterior leaflets, were attached to the mitral valve ring around its circumference. The leaflets themselves were covered on both atrial and ventricular aspects by thickened endocardium. The left ventricular endocardium was otherwise normal. Chordæ which were not thickened or shortened, were attached normally to the valve and to anterior and posterior papillary nuscles. The mitral ring, 10 cm. in circumference (normal, 10 cm.) was entirely free from myocardial attachment in its lateral half: this free half was represented by a smooth, slightly flattened cord, 2 mm. thick, to which was joined superiorly along its entire free extent, a distance of 5 cm., the septum that had incompletely partitioned the left atrium into two compartments. The circumference of the aortic valve was 7·5 cm. (normal, 7–8 cm., Parkinson, cited by Brenner, 1935).

The sac (left compartment of the left atrium) was 5·5 cm. long, 5 cm. wide and 6 cm. from front to back. It was lined throughout by thickened endocardium on which small flecks of fibrinous deposit were present low down on the posterior wall: it neither received nor gave off any vessels. The wall was 1–3 mm. thick.

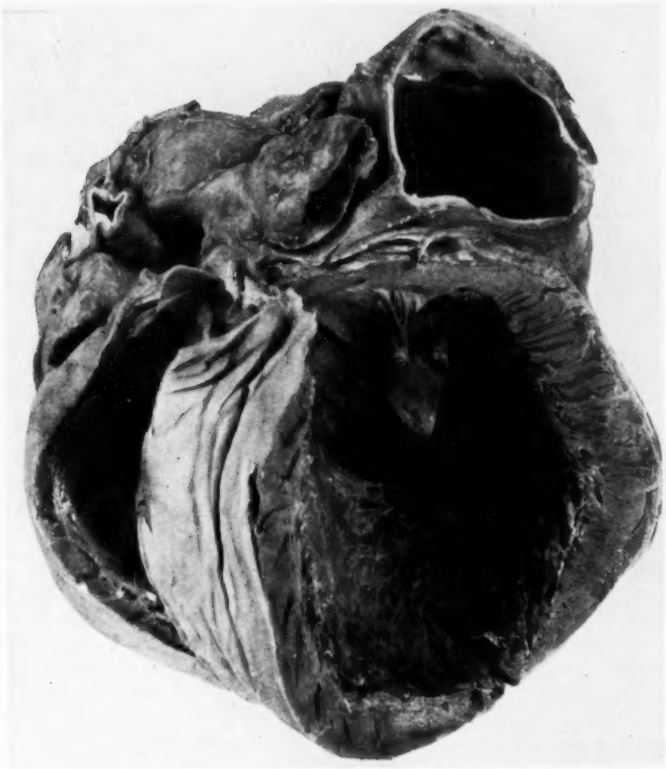

FIG. 6.—Heart with the left ventricle largely cut away, showing the dilated left atrial appendage and the sac buttressed by a pyriform mass of myocardium. The small slit situated superiorly in the sac was made for histological purposes. Case 2.

This sac was provided with two openings, one medial and one inferior. The medial opening was placed in the septum separating sac and left atrium (Fig. 7); it was oval, measuring 2·7 cm. in greatest length and 0·8 cm. in greatest width. Inferiorly, this vertically directed oval aperture stopped 0·5 cm. short of the mitral ring in its free portion, and superiorly, it fell about 3 cm. short of the sac's summit. The edges of the opening were roughened in places by fibrinous tags. No chordæ gained attachment to what otherwise looked rather like a bicuspid valve with a small anterior and a large posterior leaflet. This medial opening occupied about one-third of the septal area. The inferior opening (Fig. 8) led out of the sac into the left ventricle. When measured with the free part of the mitral valve ring displaced maximally at the right, it was 10 cm. in circumference, and oval in shape. Its medial half was formed entirely by the loose part of the mitral ring and its lateral half by a rim of thickened endocardium marking the point of junction between the sac and left ventricle. At this site no fibrous ring tissue could be identified. The inferior opening was not guarded by a valve, nor were any chordæ attached anywhere close to its margins. The pyriform buttress at the infero-lateral part of the sac (marked A in Fig. 8) consisted of solid myocardium. Fig. 8 illustrates diagrammatically the main anatomical features of this heart.

The aortic intima was slightly flecked by atheroma. The ductus arteriosus had been obliterated. The origin and distribution of the coronary arteries was normal, and they were free from atheroma. The circumflex branch of the left coronary artery was displaced downwards by the sac which received blood mainly from this vessel. Venous drainage of the heart was normal except that the sac was drained by a

FIG. 7.—Sac with wall largely cut away to show the opening in the vertical septum that divided the left atrium into two compartments. Case 2.

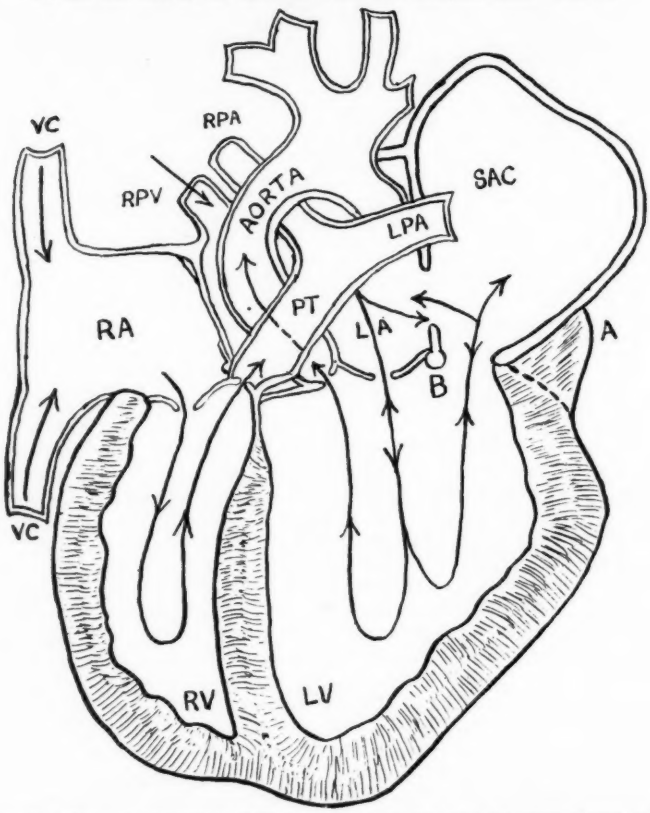

FIG. 8.—Diagram illustrating relationship between the sac (left compartment of left atrium) and rest of the heart. A is a solid myocardial buttress supporting the sac and B the mitral ring in its lateral free mobile part. Case 2.

large vein posteriorly. This vein, at its point of confluence with the coronary sinus, was marked by a fibrous intimal plaque. The pericardium was firmly adherent only over the sac and the left atrial appendage. Elsewhere it contained 150 ml. of clear fluid.

On histological examination, the presence of passive venous congestion in both greater and lesser circulations was confirmed. In the lungs there was severe intimal fibrosis involving veins and precapillary sclerosis. Arterial changes were slight, only elastic arteries being affected to any noteworthy extent by endarteritis fibrosa. Atheroma was not encountered. Sections of the liver revealed, apart from passive congestion, a few coarse fibrous trabeculæ not associated with any other abnormality. Their cause was thus obscure, but a healed massive necrosis was thought to be the probable explanation. The renal infarcts were interpreted as depending upon former thrombo-embolism originating in the sac, for here the only antemortem thrombi were found. Renal arteries, as well as pulmonary arteries, showed no more arteriosclerosis than could be attributed to chance, as comparison with controls of the same age, sex, and race showed no material differences. Sections of the heart showed endocardial fibrosis, and in places some elastosis as well, confined to the left atrium, mitral valve, and the sac wall. The sac wall in places consisted only of dense collagen lined by fibrosed endocardium, but its main component was strands of normal cardiac muscle. Similar strands were also to be found in the septum between sac and left atrium. No significant arteriosclerosis was encountered in intramyocardial branches of the coronary arteries, except for densely fibrous portions of the sac where endarteritis fibrosa was present.

Discussion

No reports of cases like those here described could be found. They are distinct from cor triatriatum, a condition characterized by horizontal partition of the left atrium into upper and lower compartments (Faber, 1934; Loeffler, 1949; Parsons, 1950; and Edwards, 1951). Cases of this anomaly, as well as division of the left atrium by a vertically directed partition or septum secundum, have been summarized by Lev (1953). Atrial anomalies due to partition of the left atrium into right and left compartments by a perforated extra septum display several variations. In the first variety the right compartment of the left atrium receives the pulmonary veins. In the second the pulmonary veins enter the left compartment, the superior vena cava the right compartment, and the inferior vena cava the right atrium. In the third variety the pulmonary veins drain into the left compartment, a left superior vena cava and the coronary sinus into the right compartment, and a superior vena cava and the inferior vena cava into the right atrium.

Although cases of a double mitral orifice are also known to occur and have been reviewed in a paper by Schraft (1950), they do not appear to have been described in association with a supernumerary left atrial chamber. Duplication of the mitral orifice is described as consisting of two orifices equal or unequal in size that present in anteroposterior or lateral relationship to one another. The accessory orifice usually lies in the anterior mitral leaflet which thus has two leaflets of its own joined to the anterior papillary muscle. On the other hand, each orifice may have one leaflet with the two orifices connected by a fibrous tissue bridge. The chordæ and leaflets have all been thickened but the valves have usually been competent. A double mitral orifice may also be displaced downward into the left ventricle. In the cases reported here, the accessory orifice had none of the features described in duplication of the mitral orifice, because in each of them it was an unguarded orifice lying lateral to the mitral ring. Cases with accessory ventricles, as anomalies distinct from ventricular diverticula, have also been placed on record, but they have not had accessory atria as well (Hemsath, 1936; Konwaler, 1944).

In Case 1 the true diagnosis could have been arrived at clinically. The radiological features suggested an outpouching in the region of the left atrial appendage, and the position of this shadow and its active pulsations related it to the cardiac chambers. Moreover, the pulsations had a paradoxical excursion showing lively expansion with each ventricular systole. This was interpreted as a mitral incompetence allowing distension of an atrial aneurysm during ventricular systole. It was difficult to explain the diastolic blowing murmur localized to the mitral area, but in retrospect this was apparently due to the diastolic emptying of the accessory sac into the left ventricle, and had the significance of this been grasped, one might have made an accurate diagnosis of an accessory atrial sac with an unguarded orifice leading into the left ventricle.

In Case 2 congestive cardiac failure together with a systolic murmur in the mitral area conducted round to the back, and the presence of a large left ventricle indicated mitral incompetence. Indeed, this patient's mitral valve was grossly incompetent at necropsy, and the diagnosis was only wrong in so far as the cause of the incompetence was not rheumatic, but detachment of the mitral ring. In neither case was the electrocardiogram sufficiently distinctive to diagnose anything more than left ventricular hypertrophy.

The bilocular sac described in Case 1 was regarded as an accessory two-chambered heart, for the following reasons. Cardiac muscle was present in the walls of both compartments, which were demarcated from one another by the A-V sulcus of the heart itself. This sulcus was occupied by the circumflex branch of the left coronary artery. Also, the orifice connecting the upper and lower compartments was situated in the same plane as the A-V sulcus. There were well formed trabeculæ carneæ present inside the lower compartment. The upper compartment was joined to the left atrium only by adhesions and since they had not been united by muscle they must be regarded as anatomically distinct. Though myocardium of the lower compartment merged with that of the left ventricle, the point of junction between them consisted of loosely woven muscle separable with greater ease than were muscle trabeculæ elsewhere. No acquired lesion was found that could explain this bilocular formation, the structure of which conformed rather with the directive influence of an organizer than the chance results of an acquired disease affecting both atrium and ventricle. The endarteritic vessels supplying the sac walls were not regarded as causal because they are usually to be found in the presence of fibrous atrophy and hypoplasia.

It is suggested that abnormal development had occurred prior to midline fusion of the endocardial tubes, but subsequent to the establishment of a single pericardium as its cavity was common to both heart and accessory chambers. The endocardial tubes that had developed from the cardiac primordia, though approximated to the midline, had fused completely only at the point where the mitral valve was ultimately to develop. The right endocardial tube subsequently gave rise to the heart itself and established normal relationships with the great vessels, whereas a smaller left tube developed only into a two-chambered heart. Fusion had not taken place at all cephalad resulting in a completely separate atrium, whereas caudad, fusion had been almost complete, producing a miniature ventricle riding upon and partially merged with the left ventricle. Endocardial cushion tissue having completed the mitral ring and its valve leaflets, would seem to have undergone canalization laterally, so providing communication with the two-chambered heart. Alternatively, the endocardial tubes had fused completely, but a second left smaller tube or endocardium-lined lacuna had persisted or had formed in addition and then established the partial fusion just described. A third explanation is that the cardiac tube had formed normally but had undergone partition into two unequal parts by a double set of interatrial and interventricular septa, so forming a four-chambered and a two-chambered heart. This is improbable, because the upper compartment of the accessory heart was entirely separate, suggesting independent development, as otherwise a septum common to both the left atrium and to this compartment should have formed. This third explanation, therefore, suffers from the complexity of requiring independent origin for the accessory left atrium and a double but unequal partition of the primitive left ventricle.

The left ventricular hypertrophy and dilatation has been ascribed to mitral valve incompetence, because its ring possessed mobility and a defect at its lateral margin. Left ventricular failure, however, had not occurred, as the lungs were not passively congested. Why the right ventricle should have undergone hypertrophy is not known, but hypertrophy was attributed to pulmonary hypertension, because arteriolar and precapillary sclerosis was present in the lungs. As the extent of the vascular changes were not thought to be severe enough to have caused the right ventricular hypertrophy by obstruction alone, they have been regarded as a result and not as a cause of the pulmonary hypertension which was possibly of primary type.

The heart in Case 2 was characterized by two chief abnormalities. An accessory septum had divided the left atrium vertically but incompetently into two compartments, and in the lateral half of its circumference the mitral ring lacked attachment to left ventricular myocardium.

It is uncertain whether this lack of attachment was congenital or acquired. Because the orifice that communicated between left ventricle and the sac had not developed a valve ring of its own, it was thought possible that the mitral ring had become stripped from the myocardium at some time after the heart had attained a definitive structure. This possibility was strengthened by the severity of the mitral incompetence which, had it been present at birth, would have led to failure before adult life. We concluded, therefore, that lateral to the mitral ring a weakness or small separation had been present and had led either to gradual stripping away of the mitral ring over a protracted time period, or to more rapid stripping shortly before death.

The accessory left atrial septum, regarded by itself, could have been another septum primum provided with an ostium secundum. This or any other view, however, must take into account the myocardial buttress (Fig. 6 and 8) situated below the level of the A-V sulcus. In this heart much will depend upon whether the buttress is accepted as accessory myocardium, or whether it is thought to have developed in fœtal life through displacement of primitive left ventricular myocardium by dilatation of the left atrial compartment. If this buttress were to be taken for an accessory hypoplastic ventricle, then it and the left atrial compartment might have been an accessory two-chambered heart that had arisen at the stage of endocardial tube fusion. This interpretation is strengthened by the previous case in which a larger but cavitated buttress was also present. Moreover, both cases had inferior apertures situated immediately lateral to the mitral valve ring.

It might plausibly be supposed that left and right tubes had merged in the usual way, but that they also underwent fusion with an accessory left endocardial tube or with a persistent left endocardial lacuna. Cephalad this lacuna then fused partially with that part of the cardiac tube destined to become the lateral wall of the left atrium. From this incomplete fusion resulted the opening that otherwise must be regarded as having formed in a second septum primum. Caudad, however, fusion with that part destined to form the lateral wall of the left ventricle was complete, producing only a pyriform mass of solid myocardium. At the site where the primitive left ventricle of the accessory heart had fused with the left ventricle, the mitral ring was prevented from establishing firm union with ventricular myocardium, so that finally it loosened to cause severe incompetence of the mitral valve.

Summary

The clinical and pathological features in two patients with developmental cardiac anomalies have been described. These particular anomalies do not appear to have been recorded before.

The first consisted of a four-chambered heart, with which a left-sided, two-chambered heart was partially merged. In retrospect, this cardiac defect might have been diagnosed during life.

The second consisted of a four-chambered heart, the left atrium of which had been vertically but incompletely divided into two compartments. The left compartment of the bipartite left atrium was supported by a pyriform buttress of solid myocardium. The bipartite left atrium might either be considered to have arisen from the formation of an accessory septum primum, or the atrial anomaly together with its myocardial buttress might have represented a partially fused two-chambered left-sided heart.

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THE VALVE OF THE INFERIOR VENA CAVA

BY

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The surgical repair of atrial septal defects (Bailey *et al.*, 1953; Gross *et al.*, 1953; Bjork *et al.*, 1954) has led to a greater awareness of the anatomy of the right atrium. In two cases of this condition we have seen an important variant involving the valve of the inferior vena cava. This structure was described by Bartolomeno Eustachius (1563), but its identity was denied by Bauhin (1605) and not mentioned by Harvey (1628). Winslow (1717) produced the first accurate description of the valve and suggested its fœtal function.

Normal Anatomy (Fig. 1). The superior and inferior venæ cavæ open into the sinus venarum which is the smooth medial and posterior wall of the atrium limited on the right side by a vertical muscular ridge, the crista terminalis. All the atrium except this area is ridged with musculi pectinati. The area between the caval orifices is convex towards the atrial cavity, the height of the convexity forming a rounded ridge, the intervenous tubercle of Lower. The oval superior caval orifice is bounded anteriorly by the crista terminalis, medially by the septum and posterior and lateral margins are continued into the wall of the atrium, the posterior in the region of the tubercle of Lower. The orifice of the inferior cava is also oval, the posterior wall being formed by the septum while it is flanked anteriorly and partly covered by the Eustachian valve or valve of the inferior vena cava (Fig. 1). This structure (Quain, 1929) is a musculomembranous semilunar fold extending posteriorly from the limbus fossa ovalis, anterior to the inferior caval orifice where it disappears. Its free border is usually membranous, concave, and directed upwards and forwards. Its adherent border is a transverse muscular ridge continuous with the anterior margin of the caval orifice. One of its surfaces is turned laterally towards the atrium and the other medially toward the vessel. It is variable in size with an average length of its free edge 3·4 cm. and average width 0·35 cm. (Yater, 1929) the latter seldom exceeding 1 cm. (Drury, 1949). It may be a simple fold or fenestrated or may consist of a network of threads or may be absent.

Anomalies consist of variations in size, extent, muscularity, and Chiari's network (Chiari, 1897), a network of fine fibres from the Eustachian or Thebesian valves to the upper portion of the crista terminalis, interatrial wall, or tricuspid valve; occasionally these may resemble chordæ tendineæ (Pan, 1936). These anomalies are most common in patients with atrial septal defects (Yater, 1929). In front of the anterior end of the Eustachian valve can be seen the circular opening of the coronary sinus which is flanked laterally by the Thebesian valve. This is variable in size, semilunar, often perforated, and usually attached to the lateral edge of the Eustachian valve.

Embryology. The right atrium of the adult heart is developed from the sinus venosus, the primitive atrium, and the right half of the atrial canal (Fig. 2). The sinus venosus opens into the right side of the primitive atrium through a vertically placed opening in the dorsal wall of that chamber, the opening being flanked by the right and left venous valves (Fig. 3). These fuse with one another above the opening in a ridge, the septum spurium. They fuse below and are continued towards the atrial canal. The orifice of the transverse part of the sinus venosus becomes drawn into the posterior wall of the right atrium, and the left valve and septum spurium fuse with the septum secundum (Arey, 1954; Quain, 1929). Bands of muscle form between the openings of the coronary sinus and inferior and superior cavæ so that the original sinus opening and right sinus valve are divided into three parts (Fig. 4): (1) the superior caval opening

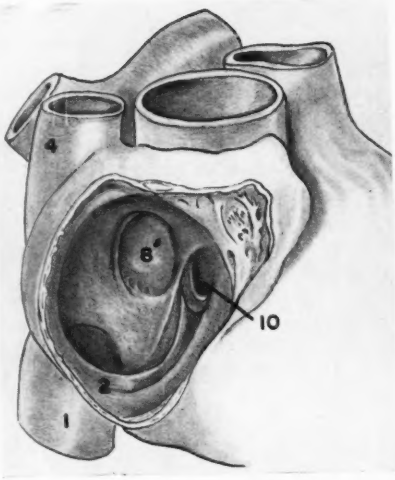

FIG. 1.—Normal anatomy of right atrium.

(1) Inf. vena cava. (2) Eustachian valve.
(4) Sup. vena cava. (8′) Fossa ovalis.
(10) Coronary sinus.

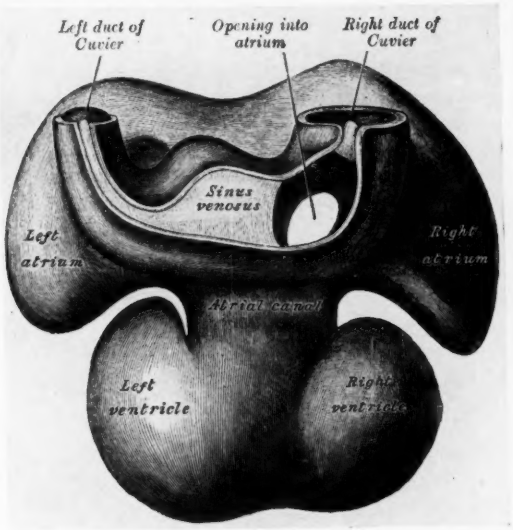

FIG. 2.—The heart of a six-weeks-old embryo, dorsal aspect. (From the model by His—*Gray's Anatomy*, 30th ed., p. 147.)

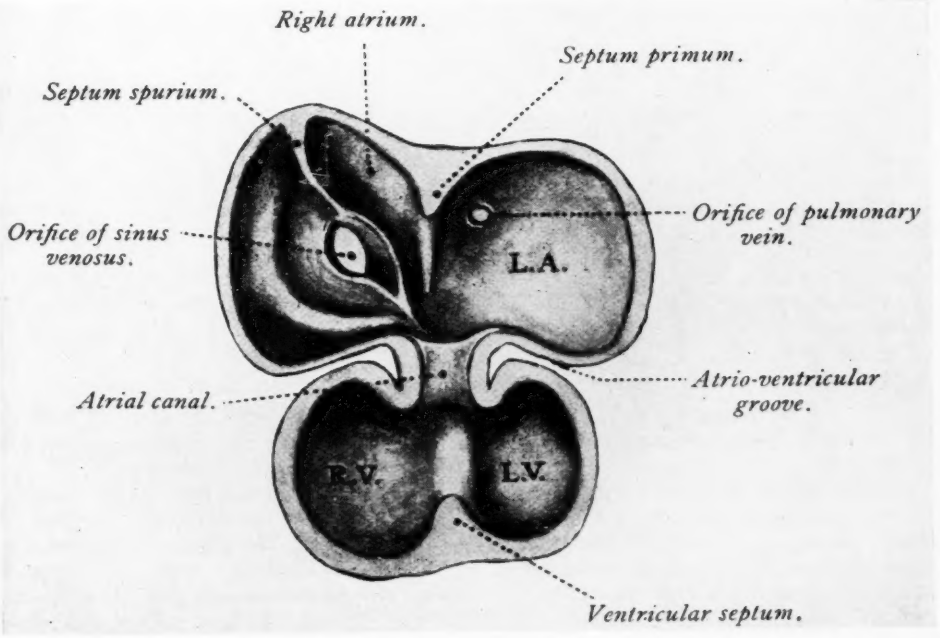

FIG. 3.—The dorsal half of the heart of a human embryo, viewed from the front. (After the model by His—*Quain's Anatomy*, 1929, Vol. VI, Part 3, p. 118.)

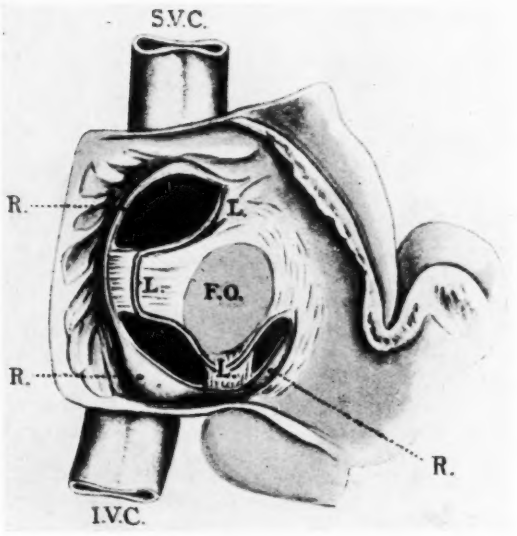

FIG. 4.—Diagram of the interior of the right atrium to show the division of the sinus opening, the fate of the sinus valves and the limbic bands. (After Keith.) R= Right venous valve, L=Left venous valve, which is carried towards the right valve by the limbic bands. F.O.=Fossa ovalis. (*Quain's Anatomy*, 1929, Vol. IV, Part 3, p. 40.)

ridged above and laterally by the remains of the upper part of the right sinus valve—the crista terminalis; (2) the inferior caval opening bounded in front by the middle half of the right sinus valve—the Eustachian valve; and (3) the coronary sinus bounded on the right by the anterior end of the right sinus valve—the Thebesian valve (Keith, 1904).

The right horn and associated area of the transverse part of the sinus venosus is gradually absorbed into the right atrium and forms the smooth-walled sinus venarum. The primitive atrium forms the auricular appendage and the area of the atrium provided with musculi-pectinati. The right half of the atrial canal forms the smooth area above the atrio-ventricular orifice.

In the fœtal heart the free concave cranial border of the Eustachian valve is directed upwards and medially and it directs the blood stream from the inferior vena cava towards the open foramen ovale (Sabatier, 1774; Barclay *et al.*, 1944).

CASE REPORTS

Case 1. A man, aged 47 years. Heart disease had been diagnosed at the age of 4 years. He gave a five-year history of progressive dyspnœa and giddiness on exertion, recurrent chest infections, left præcordial pain, with paroxysmal nocturnal dyspnœa in the last three months.

On examination there was dyspnœa at rest, central cyanosis, and raised jugular venous pressure. There was præcordial prominence with a palpable impulse over the right ventricle and pulmonary artery. Mitral systolic and mid-diastolic murmurs were present and at the pulmonary area a loud systolic click, an accentuated single second sound, and an early diastolic murmur. Scattered râles and rhonchi were heard over both sides of the chest. In the electrocardiogram there was right ventricular hypertrophy and a P–R interval of 0·24 sec. Radioscopy showed large and pulsatile pulmonary arteries, right ventricular enlargement, and a normal left atrium. Cardiac catheterization

and oximetry demonstrated a shunt from left to right and from right to left in the atrium. A pulmonary artery pressure of 105/45 was recorded and the catheter entered an anomalous pulmonary vein from the right lower lobe.

Operation. The right atrium was large and thin-walled. All the right pulmonary veins opened into the right atrium. An atrioseptopexy (Bailey *et al.*, 1953) was contemplated and three observers felt inside the atrium. The superior vena cava, anomalous pulmonary vein, and coronary sinus openings were identified. An extremely large Eustachian valve was felt but the inferior caval opening could not be located. A regurgitant jet was recognized coming from the tricuspid valve. Two defects were felt distant from the atrial wall but their margins were identified with difficulty because of the Eustachian valve. The surgeon felt at first an inferior rim to the larger defect but subsequently considered this was the crescentic fold of the Eustachian valve. Palpation of the mitral valve was not possible. Various manœuvres were tried but all caused a marked drop in oxygen saturation. Unfortunately the patient died four hours later.

Necropsy. The heart was enlarged with hypertrophy and dilatation of the right ventricle (Fig. 5). A dilated right atrium was divided into two chambers, the sinus venarum and the dilated auricular appendage, by the Eustachian valve. This structure arose on the right wall of the atrium in the

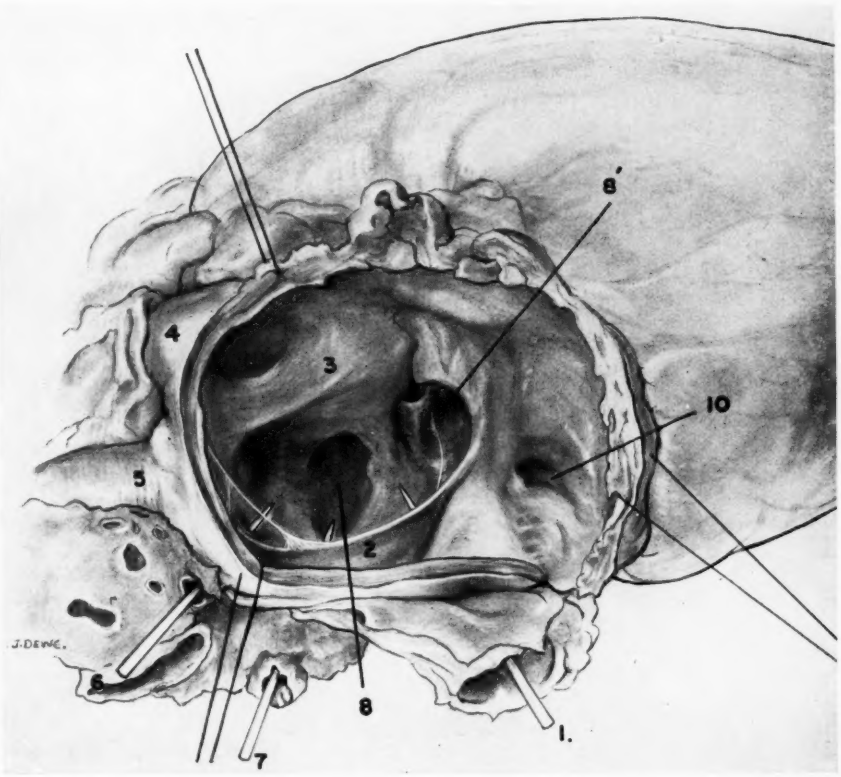

FIG. 5.—Drawing of the right atrium in Case 1. (1) Inferior vena cava. (2) Eustachian valve. (3) Tubercle of Lower. (4) Superior vena cava. (5) Superior pulmonary veins. (6) Middle pulmonary veins. (7) Inf. pulmonary veins. (8) Atrial septal defect. (8′) Foramen ovale. (10) Coronary sinus.

region of the crista terminalis, descended forwards and to the left above the opening of a normal coronary sinus and then proceeded upwards fusing with the anterior limb of the limbus fossa ovalis. It was 6·2 cm. along its free membranous edge, 2·1 cm. wide, and 0·5 cm. thick at its muscular base. The valve was perforated at the musculo-membranous junction and from its right edge arose a network of lace-like fibres which extended to the upper part of the crista terminalis, a Chiari's network (Chiari, 1837). A similar single strand extended from the left posterior aspect of the valve to the fossa ovalis. Above the fossa ovalis was a very prominent intervenous tubercle of Lower which, in combination with the Eustachian valve, produced a ring of tissue that one could readily mistake for a septal defect.

At the right end of the valve was a rounded edge between the inferior caval opening and the right inferior pulmonary vein, and above this the openings of the middle and superior pulmonary veins. On the medial wall of the atrium was the fossa ovalis with a patent foramen ovale. Above this was an atrial septal defect 2·5 cm. in diameter, with a thick rounded antero-inferior rim but no postero-superior margin. The structure of this rim was in contrast with the sharp thin edge of the Eustachian valve. The tricuspid valve was incompetent admitting four fingers but its cusps were normal. The mitral valve admitted only the finger tip, the cusps, especially the antero-medial, being fibrous. The pulmonary artery was large and the remainder of the heart was normal.

Case 2. A man, aged 27 years. Heart disease had been diagnosed at one year. There was a history of seven years of increasing breathlessness, recurrent bronchitis, once with hæmoptysis and left inframammary pain, and giddiness on exertion for seven months.

On examination there was dyspnœa at rest, central cyanosis, præcordial prominence, and a palpable impulse over the right ventricle and pulmonary trunk. There was a pulmonary systolic murmur and a split accentuated second sound. Scattered râles and rhonchi were present over both sides of the chest. In the electrocardiogram there was incomplete right bundle-branch block. Radioscopy showed right ventricular enlargement and large pulsating pulmonary arteries. A cardiac catheter passed through an atrial septal defect and also entered two anomalous right pulmonary veins.

Operation. The right atrium was dilated. Two right superior pulmonary veins entered the lower end of the superior vena cava below the azygos vein. The openings of the middle and inferior pulmonary veins were palpated within the right atrium, the latter vein being closely related to the inferior caval opening. An atrial septal defect with an antero-superior rim was identified. An atrioseptopexy (Bailey *et al.*, 1953) was performed and the oxygen saturation fell to 60 per cent (oximeter). Further manipulations raised it to 85 per cent which was 5 per cent below pre-operative level. There appeared to be a free pathway to both cavæ. Postoperatively the patient was dyspnœic and disorientated with an oxygen saturation of 60 per cent. Further cardiotomy was done and nine sutures removed without improvement, but when the tenth and most inferior suture (lying 1·8 cm. anterior to the entry of the inferior cava) was taken away the oxygen saturation rose to 95 per cent. The patient died suddenly two hours later.

Necropsy. The heart was enlarged with hypertrophy and dilatation of the right ventricle (Fig. 6). The right atrium was dilated and the Eustachian valve commenced on its right wall, descended forwards and to the left above the coronary sinus, and continued on to the medial wall in the region of the anterior edge of the septal defect. The valve was muscular, 4·7 cm. along its free edge, 1·5 cm. wide, and 0·7 cm. thick at its base. On the medial wall of the atrium was a septal defect 3 cm. in diameter with a definite rounded firm postero-superior rim. This passed down the posterior auricular wall to disappear behind the medial end of the Eustachian valve so that the valve and the absent ring of tissue were closely related. The ease with which the two could be confused explained the operative difficulties. Two right superior pulmonary veins entered the superior vena cava below the azygos vein and the middle and inferior veins opened into the postero-lateral wall of the atrium. The pulmonary artery was dilated and the remainder of the heart was normal.

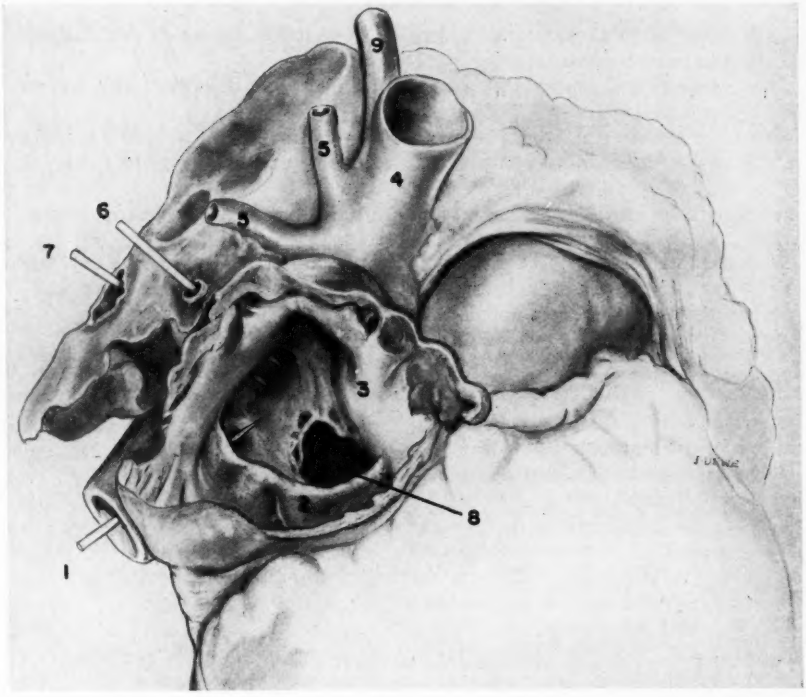

FIG. 6.—Drawing of right atrium in Case 2. (1) Inferior vena cava. (2) Eustachian valve. (3) Tubercle of Lower. (4) Superior vena cava. (5) Superior pulmonary veins. (6) Middle pulmonary veins. (7) Inferior pulmonary veins. (8) Atrial septal defect. (9) Azygos vein.

DISCUSSION

Lancisi (1717) suggested that the Eustachian valve directed the superior caval stream away from the inferior cava in upright homo sapiens. Franklin (1948) stated that it persists only in hearts in which an element of the superior caval flow is directed towards the inferior caval orifice, there being a direct correlation between the height of the valve and the direction of the superior caval flow. In the fœtus it directs inferior caval blood across the foramen ovale (Sabatier, 1774; Barclay *et al.*, 1944) and recently Swan *et al.* (1954) have suggested that right-to-left shunts are associated with the relationship of the atrial septal defect to the inferior caval stream. Persistence of the valve is more common in atrial septal defects (Yater, 1924) and may occur with Ebstein's disease (Taussig, 1947). These facts suggest a relationship to stream effects in the atrium and it may play a part in right-to-left shunts in the atrium. Several observers (Yater, 1929; Jordan, 1926; Salviati, 1945) have reported thrombi and secondary emboli in association with the valve and Chiari's network. The latter may cause arrhythmias (Yater, 1929; Jordan, 1926). A large valve may interfere with catheterization of the coronary sinus (Bing *et al.*, 1951) or the inferior cava.

In Case 2 the valve formed a false lower rim to a defect that had no lower edge. Lewis (1955) has reported a similar arrangement in four patients. The danger of including this valve in atrial septal repairs is obvious unless it is identified by its thin sharp edge and relationship to the inferior caval opening.

Summary

The surgical repair of atrial septal defects has led to an increasing awareness of the anatomy of the right atrium and its variations.

The normal anatomy and embryology of the right atrium is described with emphasis on the valve of the inferior vena cava.

Two patients are described in whom surgical repair of atrial septal defects was attempted. In both, the valve of the inferior cava made the anatomy difficult to interpret and surgery was unsuccessful.

This valve should be identified in the repair of atrial septal defects and suggestions are made for doing this.

The valve of the inferior vena cava may play a part in right-to-left shunts and in stream effects in the atria. It may cause failure to catheterize the coronary sinus and inferior vena cava, and lead to thrombotic and embolic phenomena, and arrhythmias.

My thanks are due to Mr. N. R. Barrett and Mr. G. K. Harrison for permission to publish these cases; to Dr. T. Morris for help with the anatomy and embryology, and to Miss Joan Dewe and the Department of Medical Photography for the illustrations. In particular I am grateful to Dr. Raymond Daley for his advice and encouragement.

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LEFT ATRIAL, "PULMONARY CAPILLARY", AND ŒSOPHAGEAL BALLOON PRESSURE TRACINGS IN MITRAL VALVE DISEASE

BY

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In selecting patients for mitral valvotomy, the exclusion of mitral insufficiency by common clinical methods has proven unreliable. We endeavoured to determine whether preoperative " pulmonary capillary " pressures and tracings taken by means of a balloon in the œsophagus at the left atrial level would be of value in the diagnosis of mitral insufficiency. Pressure pulses were also obtained directly from the left atrium at operation; their characteristics in mitral stenosis and mitral insufficiency were studied, and they were correlated with the " P.C." and œsophageal balloon tracings, since the latter two are of value only in so far as they reflect hæmodynamic events within the left atrium. To accomplish these aims, we set out to obtain all three types of tracing in each of a series of 30 patients who were operated upon for the relief of mitral stenosis.

We relied upon the surgeon's finger to detect insufficiency. Both the size of the mitral orifice and the presence of a regurgitant jet were taken into consideration (Wynn *et al.*, 1952). These criteria may be inadequate but must serve until better ones are devised.

Historical Review

Left atrial pressure pulses in the patient with mitral stenosis were first recorded by Munnell and Lam (1951). Wynn *et al.* (1952) reproduced and analyzed a large number of left atrial curves taken at operation in patients with normal hearts and with mitral valve lesions, and concluded that the normal left atrial pressure pulse resembled that in the right atrium except that the amplitude of the late systolic wave (which will be called the " V " wave) was greater on the left side. Patients with pure mitral stenosis and sinus rhythm showed left atrial tracings resembling the normal, although the level of pressure was higher. When auricular fibrillation was present, the pressure rose sharply at the onset of ventricular contraction and there was little or no drop in early systole such as occurred in sinus rhythm (the " descent of the base " of the heart). That this early systolic pressure rise did not necessarily indicate mitral insufficiency was attested to by the fact that the rise was greatest when the preceding diastole was shortest. That is, it was inversely proportional to the completeness of ventricular filling and therefore perhaps dependent upon the distention of the auricle. In the presence of mitral stenosis, mitral insufficiency did not produce any constant qualitative change in the form of the left atrial pressure tracing. However, one patient with mitral insufficiency and sinus rhythm showed a pressure rise in late systole of 25 mm. Hg, higher than in any case of pure mitral stenosis.

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In a group of left atrial pressure pulses taken by the transbronchial route, Facquet *et al.* (1954) confirmed most of Wynn's findings but attributed more importance to a high V wave as an indication of mitral insufficiency. When rapid auricular fibrillation was present, however, a high V wave had no such significance, according to Facquet. A high V wave was also found in a patient with left ventricular failure without mitral valve disease. Unfortunately, there was no surgical or post-mortem confirmation of the diagnosis of mitral insufficiency in this group of patients.

Left atrial, and in most cases left ventricular, pressure pulses, were recorded by Venner and Holling (1953) in a series of patients with mitral valve disease coming to operation. These authors concluded that mitral insufficiency did not lead to characteristic changes in the left atrial tracings, presumably because the volume of regurgitant blood was small in comparison with the volume of the left atrium and the pulmonary veins.

" *Pulmonary capillary* " *Pressures.* The concept that a pulse wave reflected from the left atrium may be recorded from the distal end of a severed branch of the pulmonary artery apparently originated with MacCallum and McClure (1906). These authors produced mitral insufficiency in animals and demonstrated a regurgitant pressure wave in the left atrium and in the transected pulmonary artery " receiving pressure from the lung only." Hellems *et al.* (1948, 1949) by wedging a cardiac catheter into a distal branch of the pulmonary artery, obtained what they termed " pulmonary capillary " pressures in animals and man. Lagerlöf and Werkö (1949) confirmed and further characterized such pressures, while Dow and Gorlin (1950) demonstrated that mean pressures in the " P.C." tracings were reliable indices of left atrial mean pressure in dogs. Gorlin *et al.* (1951) and Lagerlöf and Werkö were the first to suggest that it might be possible to diagnose mitral insufficiency from the " P.C." tracing (i.e. by the finding of a high late systolic wave).

There have been subsequent reports by van Bogaert *et al.* (1952), Werkö *et al.* (1953), Allison and Linden (1953), and Björk (1954) for and against the concept that the two pressures mirrored each other both in form and in absolute value in patients with mitral valve lesions. Simultaneous or immediately consecutive pressure tracings by Connolly *et al.* (1953) and by Epps and Adler (1953), using the bronchoscopic method, left little doubt, however, that in patients with mitral valvular lesions the " P.C." pressures correlated closely with the direct left atrial pressure. Connolly *et al.* were unable to distinguish mitral stenosis from mitral insufficiency on the basis of " wedge pressures." They found that most patients with mitral insufficiency showed high V waves, but many cases of pure mitral stenosis also had them, and one patient with mitral insufficiency did not. They found a fairly constant delay amounting to 0·05 sec. of the " P.C." compared to left atrial tracings. Epps and Adler added the observation that C waves were present but small in left atrial pressure curves but that these were less evident in " P.C." tracings.

A comparison of " P.C." with direct left atrial curves led Wolter *et al.* (1953) to conclude that there was good correspondence between the two. They stated that it might be possible to recognize even mild degrees of mitral insufficiency from the " P.C." curve and that one of the important criteria was the failure of the pressure to drop to the base line during systole. They recognized, however, that when auricular fibrillation was present this finding was of no significance.

When mitral stenosis was combined with mitral insufficiency, Soulié *et al.* (1954) found that the " P.C." pressure pulse was suggestive of mitral insufficiency only when the jet found at operation was of considerable size. In most cases the V wave was high and sharp, particularly when sinus rhythm was present.

Œsophageal Balloon Tracings. Left atrial pulsations have been recorded by means of a balloon in the œsophagus for many years (Minkowski, 1907; Rautenberg, 1907). Lasser and co-workers (1952) revived the method, using a fluid-filled system and modern equipment, and demonstrated the resemblance between what they termed the " œsophageal piezocardiogram " and direct left atrial pressures in animals under varying conditions, and with experimentally produced valvular lesions: they described such tracings in subjects with normal hearts and with mitral valve disease. Mitral stenosis was characterized by a sharp, early systolic peak, whereas mitral insufficiency

showed a later systolic pressure rise. With combined lesions they found an early systolic pressure peak followed by a secondary rise later in systole. No direct left atrial pressures were available in these cases, however.

Van den Heuvel-Heymans (1952), using Lasser's technique, compared the œsophageal balloon tracings with direct left atrial pressure pulses taken at operation in the same patients, confirming the basic similarities between the two. Characteristic alterations of both œsophageal balloon and direct left atrial pulses were observed in mitral valve disease. Thus, he reported that a single-peaked high V wave, higher than the C wave, was characteristic of pure mitral insufficiency. He also attributed diagnostic significance to the pressure drop after the C wave, stating that it was smaller in combined stenosis and insufficiency than in pure stenosis. This paper contains one illustration showing the resemblance between " P.C.," œsophageal balloon and direct left atrial pressure pulses in a single case.

Abelmann *et al.* (1953) found a positive systolic wave which they considered characteristic for mitral insufficiency, although the same pattern was also found in some cases of mitral stenosis in whom no regurgitant jet was found at operation. This, they claimed, tended to confirm the contention that most patients with mitral stenosis have some mitral regurgitation.

A large number of patients with and without heart disease were studied by Zoob (1954) but he used a more compressible system which was apparently filled with air rather than liquid. His tracings are therefore not strictly comparable with those mentioned or with ours, which were all obtained with liquid-filled systems. Zoob attached diagnostic importance to the fact that in pure mitral incompetence the apex of the V wave preceded the second heart sound, but concluded that the diagnosis of incompetence in the presence of mitral stenosis was difficult.

Material

Thirty patients were studied. They ranged in age from 28 to 50 years. There were 22 women and 8 men. On the basis of complete clinical, electrocardiographic, and radiologic studies, 27 of these patients were thought to have pure mitral stenosis. Of the remaining three, in whom the presence of mitral insufficiency was also suspected, two proved to have this lesion at the time of thoracotomy, and valvotomy was not performed. Mitral insufficiency of significant degree was also found in three patients in whom it was not suspected. Three patients with absent or minimal mitral incompetence before valvotomy, developed marked regurgitation afterwards.

It need scarcely be emphasized that this group of cases was carefully selected before operation to eliminate those with mitral insufficiency. To the degree that we were successful in this, our study suffers from a paucity of patients with this lesion.

Cardiac catheterization was performed in 27 of these 30 patients. Œsophageal balloon tracings were obtained in all. Direct left atrial pressure pulses were obtained during surgery in all before valvotomy, and in most afterwards. In some cases left atrial, left ventricular, and aortic pressure pulses were obtained simultaneously on the same ordinate scale and with manometers of the same sensitivity (Gordon *et al.*, 1954). " P.C." and œsophageal balloon tracings were taken several days before operation.

Methods

Statham (P23 A) pressure transducers were used throughout. In the first 15 cases a four-channel direct-writing instrument was used in which a heated stylus recorded on heat-sensitive paper. The paper speed of this instrument was 25 mm. per second. In the latter half of the studies we used a four-channel cathode-ray photographic recording system* for three pressure channels and simultaneous electrocardiogram. Paper speed was either 25 or 50 mm. per second. We used the latter almost exclusively. The reference electrocardiogram was almost always lead II.

Left atrial pressures were taken by means of a 20 gauge, short bevel needle 3·7 cm. long, thrust

* Made by Electronics for Medicine, Inc., New York, N.Y.

through the atrial appendage. The needle was connected to the pressure transducer by a length of lead or thick plastic tubing, fitted with Luer adapters. The lead was 8 mm. in outside diameter and 3 mm. inside diameter. The vinyl plastic measured 7 mm. in outside diameter, with a bore of 1·75 mm.* The zero point for the manometers was at the mid-atrial level as determined in the open chest.

Pulmonary capillary pressures were obtained during cardiac catheterization by the standard technique of Hellems *et al.* (1949). With rare exceptions, 8F catheters were used, 125 cm. long and with bird's-eye tips. The zero point for pressures was 5 cm. below the angle of Louis with the patient supine. In most cases these pressures were recorded during quiet respiration. Criteria for " P.C." pressures were: (1) the contour of the tracing, which was distinctly different from that of the pulmonary artery in the same patient; (2) the characteristic snapping back of the catheter when its tip was gradually withdrawn, indicating that it had been tightly wedged; (3) in many cases when attempts were made to aspirate blood either no blood could be obtained, or that which was obtained was fully saturated with oxygen.

The *œsophageal balloon* was made from a cylinder of latex cut from the finger of a surgical glove, fixed on to a length of polyethylene tubing† about 10 cm. from its tip. This tubing had an outside diameter of 4 mm. and inside diameter of 3 mm. The entire system was filled with a mixture of water and sufficient 35 per cent Diodrast to permit fluoroscopic visualization of the balloon. Bubbles were eliminated from the system as much as possible, although a tiny one usually remained. When inflated, the balloon measured 3·1 cm. long and was of the same diameter. The distance from the proximal end of the balloon to the stopcock on the end of the polyethylene tube varied in different balloons from 1·2 to 1·5 metres. The longer tubes were more convenient to work with, although possibly introducing a slight error in timing. In order faithfully to record left atrial events the balloon must be relatively small, otherwise the tracings will be distorted by pressure or volume changes taking place at other than the desired left atrial level.

The patient's oropharynx was anæsthetized with a 2 per cent pontocaine spray and the balloon was passed into the œsophagus in a deflated condition. It was then inflated with 5–15 c.c. of the water-diodrast mixture, and could then be placed at the left atrial level under fluoroscopic control. Tracings were made at various levels, and with different degrees of inflation, with the patient erect. It was usually necessary to suspend respiration while the records were being made. No attempt was made to measure absolute pressures from these tracings, as the amplitude of the pressure pulse is a function of the elasticity of the system, the amount of fluid in the balloon and the initial pressure within it, as well as the intra-atrial pressure.

Left Atrial Pressures

Of the three types of pressure pulse under study, direct left atrial pressures were the easiest to obtain, measure, and interpret, and showed the fewest artefacts. Only when thrombus material was present in the left atrium were we unable to obtain satisfactory curves. Respiratory variations were rarely observed, presumably because of the open chest. Our findings agree very closely with those of Wynn *et al.* (1952).

Normal Left Atrial Pressures. We were able to study only a few left atrial pressures in normal hearts. These were obtained simultaneously with left ventricular and aortic curves, and recorded with manometers of the same sensitivity with identical base-lines, as part of another study. Mean pressures in these left atrial control pressures averaged less than 10 mm. Hg. A, C, and V waves could be identified, the first usually higher than the second, and the V wave usually the highest of all, occasionally reaching a peak level of 12 mm. Hg. Because of the lower general level of pressures, artefacts, presumably due to motion of the plastic tubing, were occasionally more troublesome than in the cases with mitral valve disease.

* Made by U.S. Catheter and Inst. Co., Glens Falls, N.Y.
† P.E. 350, Clay Adams Co., N.Y.

Mitral Stenosis, Sinus Rhythm. Eleven patients fell into this category (Fig. 1, 2, and 3). The pressure pulses showed considerable variation, but in general were similar to the normal, except that the pressure level was considerably higher. Thus, the mean pressures averaged 27 mm. Hg, the highest measuring 43 mm. and the lowest 8 mm. The highest point of pressure recorded in any of our cases occurred in a patient in this group, the peak of whose V wave measured 60 mm. The left atrial pulse pressures averaged 16 mm.

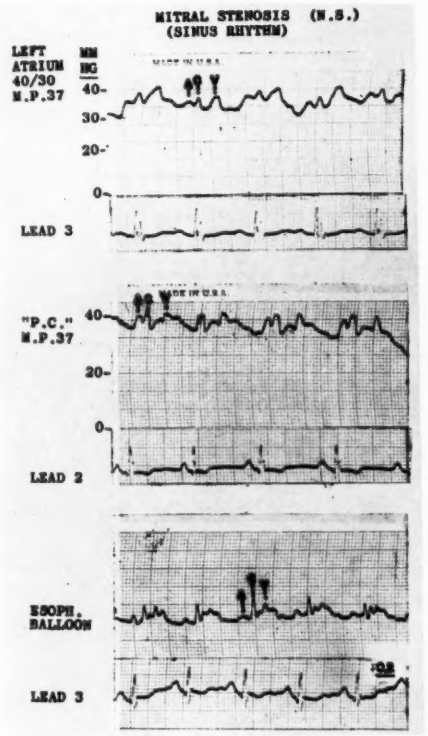

FIG. 1.—A patient with mitral stenosis and sinus rhythm, in whom all three tracings were similar. Note the irregularity of the V wave in the " P.C." and balloon tracings. (Paper speed = 25 mm. per second.)

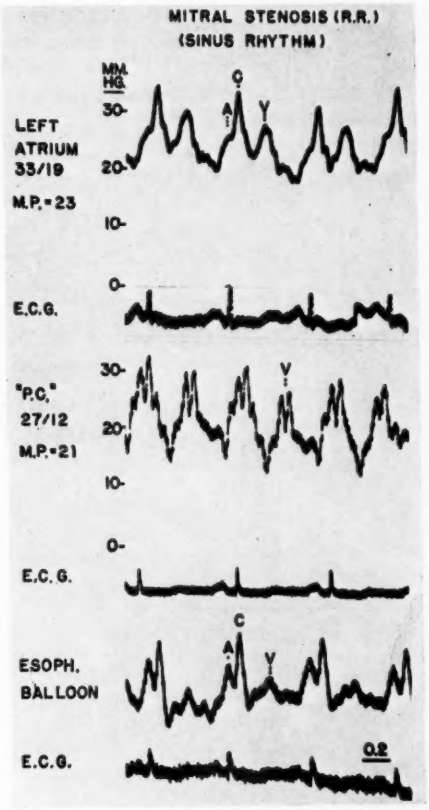

FIG. 2.—Note the strong resemblance between the left atrial and œsophageal balloon pressure pulses. (Paper speed = 50 mm. per second. E.C.G. = lead II unless otherwise indicated.)

None of the three waves was consistently higher than the others in this group. The C wave often occurred on the upstroke or down stroke of the A wave, so that the point of onset of these waves often could not be determined for purposes of timing. Sometimes, particularly when artefacts were present, the C wave could not be identified. The V wave was usually a single large wave but occasionally was split. In several cases it was much higher than the A and C waves.

Mitral Stenosis, Auricular Fibrillation. Eleven cases fell into this category (Fig. 4). The mean pressures averaged 24 mm. Hg with a range from 11 mm. to 35 mm. Hg. The highest point of

pressure in this group was a V wave 45 mm. high. The left atrial pulse pressures averaged 12 mm. Hg. As described by Wynn, the A wave was absent, the pressure rose abruptly with the C wave and dropped only slightly thereafter, giving a plateau-like appearance, in which the C wave formed the first hump and the V wave the last. The C and V waves were usually about the same height but occasionally the V wave was much higher. The height of the plateau pressures varied inversely with the length of the preceding diastole, i.e. it tended to be lower with more complete left atrial emptying. Arrhythmias other than auricular fibrillation gave rise to a similar picture depending on the time of atrial contraction. For instance, in nodal rhythm, the C and A waves were usually summated.

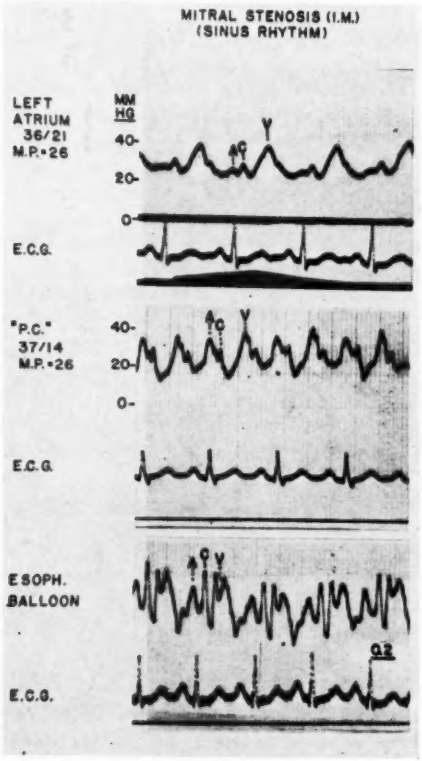

FIG. 3.—The left atrial pressure pulse in this patient with pure mitral stenosis shows a tall V wave. (Paper speed = 50 mm. per second.)

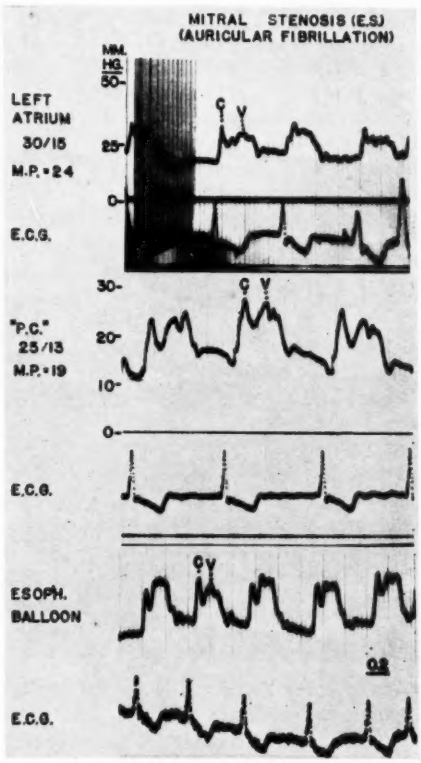

FIG. 4.—In this case of mitral stenosis with auricular fibrillation all three tracings show striking resemblances. (Paper speed = 50 mm. per second.)

Mitral Stenosis and Insufficiency, Sinus Rhythm. Only two of our patients had combined mitral stenosis and insufficiency, with sinus rhythm. In one case, in which the jet was described as minimal, the pressures were 35 mm. Hg maximum and 17 minimum, with a mean pressure of 26 mm. This curve did not differ in any way from that found in pure mitral stenosis. In the second case with moderate mitral insufficiency the left atrial pressures amounted to 40/25 mm. Hg, mean pressure 32 mm. and pulse pressure 15 mm. Although the V wave was prominent in this patient, the curve dropped to the base line after the C wave (Fig. 5).

Mitral Stenosis and Insufficiency, Auricular Fibrillation. Four patients with auricular fibrillation showed minimal to moderate regurgitant jets at operation as appreciated by the surgeon's finger. In one of these, although a satisfactory curve was obtained, only the pulse pressure could be measured, for technical reasons. In one other, only the mean pressure was obtained. The average of the three mean pressures was 29 mm. Hg. The average of the pulse pressures in the three cases where it could be measured, was 9 mm. Hg. In three of the four patients, the curves could not be distinguished from those of pure mitral stenosis; in the fourth the V wave was higher than that usually found in mitral stenosis alone.

Mitral Insufficiency without Stenosis. In the one patient with sinus rhythms (Fig. 6), valvulotomy was not performed. The left atrial pressure was 30/17, with a mean pressure of 23 mm. Hg and pulse pressure of 13 mm. Hg. The curve did not differ from the others in any important respect. The one patient with auricular fibrillation (Fig. 7) had a left atrial pressure

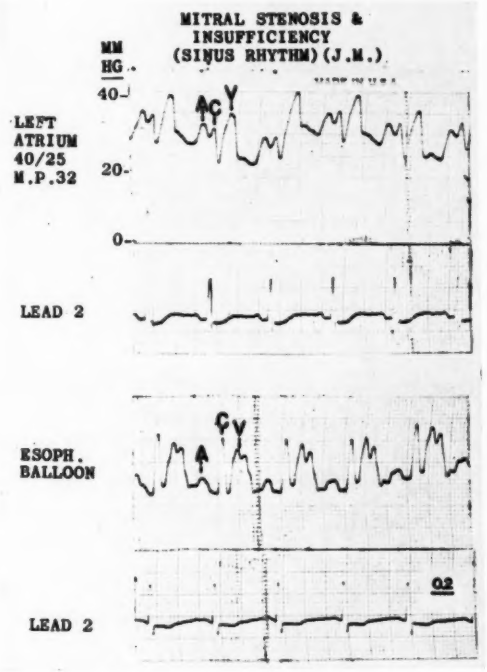

FIG. 5.—See text for description. (Paper speed = 25 mm. per second.)

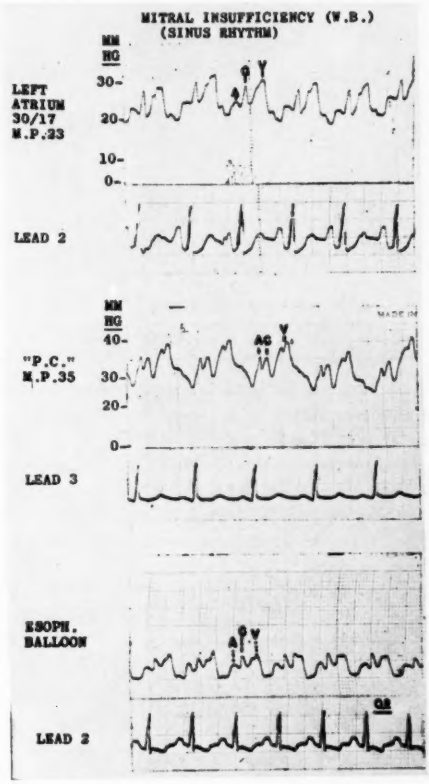

FIG. 6.—See text. (Paper speed = 25 mm. per second.)

of 55/35 with a mean of 40 mm. Hg and pulse pressure of 20 mm. Hg. The tracing was of the plateau type but with a gradual rise in pressure from the C to the peak of the V wave. The late systolic rise in pressure would suggest mitral insufficiency according to previously proposed criteria.

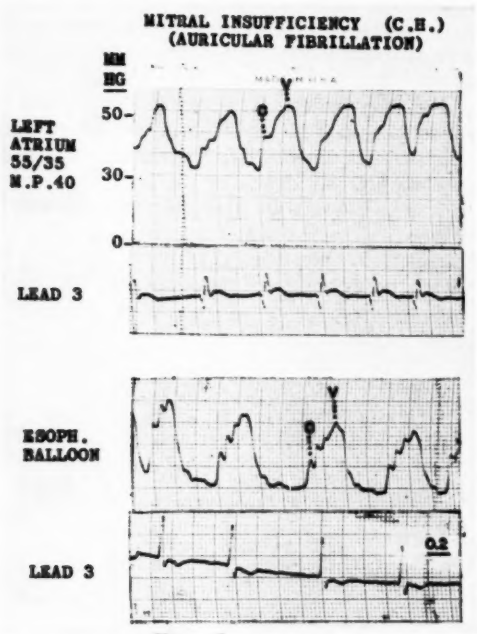

FIG. 7.—See text. (Paper speed = 25 mm. per second.)

However, we have mentioned before that this type of tracing may occur in pure mitral stenosis when associated with auricular fibrillation.

Mitral Insufficiency developing after Valvotomy. Three patients developed strong regurgitant jets after the valve was widened where previously insufficiency had been slight or absent. In one of these the left atrial tracing taken after valvotomy was exactly the same as that obtained before, showing A and V waves of equal amplitude. In the second, a patient with auricular fibrillation (Fig. 8) the V wave became much higher after valvotomy and the slight drop in pressure after the C wave, which was present before valvotomy, disappeared. In the third patient (Fig. 9) the changes were of special interest. The mean left atrial pressure rose after valvotomy from 24 to 26 mm. Hg. This rise was attributable chiefly to a rise in the height of the V wave, from 32 to 37 mm. Hg, whereas the peak of the A wave *dropped* from 23 to 19 mm. Hg and the C wave from 28 to 26. Further analysis of these curves showed that the mean systolic pressure rose, while the mean diastolic pressure dropped slightly. The mean diastolic gradient between atrium and ventricle dropped from 20 to 14 mm. Hg, chiefly because of a rise in the diastolic pressure in the ventricle. The pressure tracings, therefore, confirmed the surgeon's opinion that the mitral stenosis was relieved but that mitral insufficiency was produced. It is of interest that all three of these patients were worse after operation than before.

Summary of Left Atrial Pressure Findings. The pressure pulses in mitral stenosis were no different from the normals except that the pressure level was higher. With auricular fibrillation the A wave was absent and the C and V waves formed a plateau. The cases of mitral insufficiency were too few to allow final conclusions but they tended to show an increase in the height of the V wave and more sustained pressure between the C and V waves, in both sinus rhythm and auricular fibrillation. The height of the left atrial pulse pressure was of no diagnostic importance. None of the previously

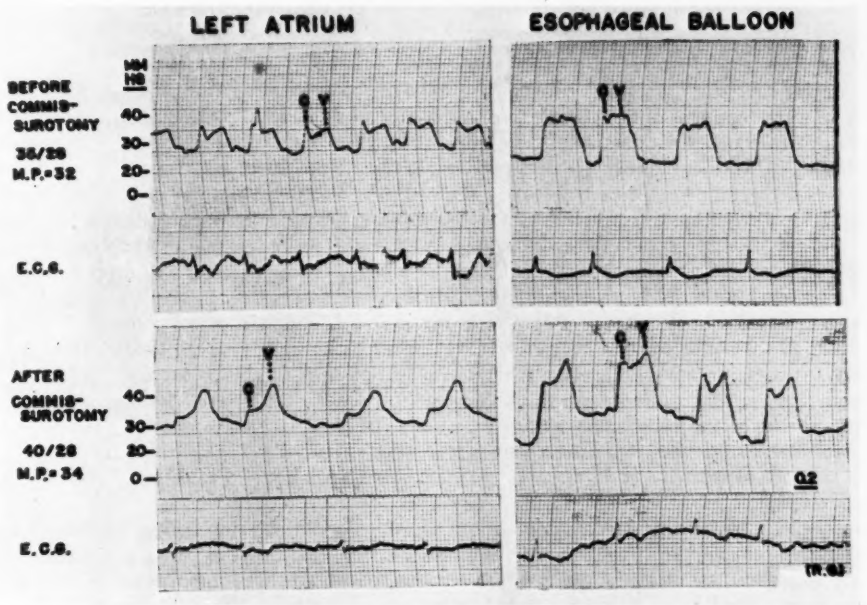

FIG. 8.—Tracings taken before and after valvotomy in a patient who developed a strong regurgitant jet as the result of surgery.

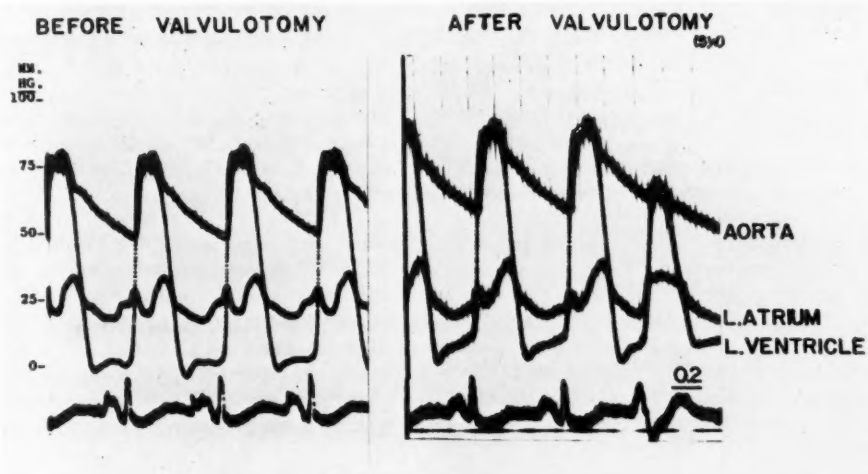

FIG. 9.—Simultaneous left atrial, left ventricular, and aortic pressure pulses before and after valvotomy in another patient who developed mitral insufficiency after surgery. Described in text. (Paper speed = 50 mm. per second.)

proposed criteria were of much help in establishing the presence of mitral insufficiency, either when alone or in combination with mitral stenosis.

" Pulmonary Capillary " Pressures

These were the most difficult both to obtain and to interpret. " P.C." pressures could be obtained in only 19 of 27 patients who had cardiac catheterization. In three of these, the curves were non-phasic, constituting either mean pressures or mean pressures with superimposed artefacts. Difficulties in obtaining satisfactory " P.C." curves have been encountered by others (Venner and Holling, 1953). A failure to obtain " P.C." curves in eight patients was attributed to a variety of causes; most often the catheter formed a loop in the right auricle or main pulmonary artery when attempts were made to wedge the tip. In at least two patients the catheter was properly wedged but the tracings were pulmonary artery tracings.

Thus, difficulties in obtaining " P.C." pressures may be divided into two categories: (1) a group that could probably be eliminated by improvements in technique (Wood, 1953); and (2) a group in which for some unknown reason, it is impossible to obtain " P.C." pressures. We attempted to determine whether there was any common denominator among the latter. We found no correlation with the height of the pulmonary artery pressure or with the clinical picture. However, of the 15 patients with auricular fibrillation who were catheterized, the " P.C." pressures were unsatisfactory in nine, whereas in the 12 patients with sinus rhythm, only two were unsatisfactory, a much lower percentage.

Even when " P.C." pressures were obtained, they contained numerous artefacts, probably mainly due to movement of the catheter within the beating heart. These artefacts made it difficult, in many instances, to define the onset of the various waves, so that for purposes of timing hæmodynamic events the "P.C." pressures were the least satisfactory.

Normal " P.C." Pressures. The normal human "P.C." pressure pulse may show considerable variation from case to case, but consists, in its ideal form of A, C, and V waves differing in no essential details from the left atrial pressure pulse, with the exception of a slight delay in transmission. Because of artefacts of catheter movement, and damping within the catheter manometer-recording system, the C wave often cannot be identified. The relative heights of the A and V waves may vary.

" P.C." Pressure in Mitral Valve Disease. When one takes into consideration that they were obtained at different times and under different conditions, the resemblance between " P.C." and left atrial curves was good (Fig. 1, 4, and 6). There were, however, many exceptions (Fig. 3) so that, in a given case, the left atrial curves could not be predicted from the " P.C." with any assurance. In 17 cases where both " P.C." and left atrial pressures were obtained, they resembled each other in 10. A comparison of mean pressures in the " P.C." and left atrium (Table I) showed fair correlation, with no systematic deviations related to the cardiac rhythm or the nature of the valvular lesion.

As in the normal " P.C." pressure pulse, the C waves were often impossible to identify when sinus rhythm was present. However, in auricular fibrillation the pressure rise with the onset of systole was often abrupt and clear (Fig. 4). When the V wave was prominent in the left atrial tracing, this was often reflected in the " P.C." although in the latter it was often split. As compared with corresponding waves in the left atrial tracings (Table II), our " P.C." curves showed a fairly constant delay of 0·05 sec. This is essentially the same figure reported by Connolly *et al.* (1953) (0·05 sec.) and by Wolter *et al.* (1953) (0·06 sec.).

In no instance did we find the " P.C." tracing of any value in the preoperative diagnosis of mitral insufficiency.

Œsophageal Balloon Pressure Pulses

From the technical standpoint satisfactory curves were obtained in every instance. The procedure, however, was time consuming and proved to be distressing to the patient. This is reflected

TABLE I

DIRECT LEFT ATRIAL, AND "P.C." PRESSURES IN 30 PATIENTS OPERATED UPON FOR MITRAL STENOSIS

Patient	Age	Sex	Surgical diagnosis	Rhythm	Left atrial pressures (mm. Hg)				"P.C." pressures (mm. Hg)			
					Max.	Min.	Mean	Pulse pressure	Max.	Min.	Mean	Pulse presure
J.S.	33	F.	M.S.	S.R.	60	38	43	22	45	15	34	30
N.S.	39	M.	M.S.	S.R.	40	30	37	10	40	34	37	6
A.B.	50	F.	M.S.	S.R.	47	25	28	22	43	20	31	23
S.P.	31	M.	M.S.	S.R.	33	24	27	9	30	12	19	18
R.R.	42	F.	M.S.	S.R.	33	19	23	14	27	12	21	15
E.D.	37	F.	M.S.	S.R.	13	3	8	10	N.C.			
E.K.	29	F.	M.S.	S.R.	42	23	33	9	30	16	22	14
P.B.	24	F.	M.S.	S.R.	35	15	28	20	30	15	24	15
L.R.	32	F.	M.S.	S.R.	33	16	26	17	43	16	30	27
G.H.	36	F.	M.S.	S.R.	39	20	25	19	N.O.			
I.M.	34	F.	M.S.	S.R.	36	21	26	15	37	14	26	23
El. C.	39	F.	M.S.	A.F.	45	22	30	23	40	34	38	6
E.M.	32	F.	M.S.	A.F.	27	18	21	9			30	
F.G.	36	F.	M.S.	A.F.	44	32	35	12	N.O.			
J. di G.	49	F.	M.S.	A.F.	40	25	32	15	N.O.			
E.H.	37	F.	M.S.	A.F.	32	18	25	14	N.O.			
R.L.	33	F.	M.S.	A.F.	20	9	15	11			28	
G.B.	32	F.	M.S.	A.F.	30	22	27	8	24	15	22	9
S.Pa.	37	F.	M.S.	A.F.	38	19	28	19	N.O.			
A.K.	37	F.	M.S.	A.F.	16	6	11	10	N.C.			
E.S.	31	F.	M.S.	A.F.	30	15	24	15	25	13	19	12
M.G.	42	F.	M.S.	A.F.	17	9	13	8	24	11	16	13
J.M.	33	M.	M.S. & M.I.	S.R.	40	25	32	15	N.O.			
S.W.	45	M.	M.S. & M.I.	S.R. & A.F.	35	17	26	18	N.O.			
F.C.	30	M.	M.S. & M.I.	A.F.	42	30	38	12	28	18	26	10
H.C.	46	M.	M.S. & M.I.	A.F.			18		N.O.			
R.G.	41	F.	M.S. & M.I.	A.F.	35	28	32	7			18	
E.C.	39	M.	M.S. & M.I.	A.F.				8	33	17	31	16
W.B.	28	M.	M.I.	S.R.	30	17	23	13	40	25	35	15
C.H.	42	F.	M.I.	A.F.	55	35	40	20	N.C.			

M.S.= Mitral stenosis S.R. = Sinus rhythm N.O. = Not obtained
M.I. = Mitral insufficiency A.F. = Auricular fibrillation N.C. = Not catheterized

TABLE II

TIME BETWEEN QII AND ONSET OF C WAVE IN PRESSURE PULSES*

Patient	Diagnosis	Rhythm	QII to onset of C wave (seconds)		
			Left atrium	"P.C."	Œsoph. balloon
G.B.	M.S.	A.F.	0·05	0.10	0·04
I.M.	M.S.	S.R.	0·05	0.10	0·06
E.S.	M.S.	A.F.	0·05	0·10	0·05

* No correction made for time of passage of pulse wave through catheter or polythene tubing.

in the fact that the heart rate was much more rapid during the œsophageal balloon procedure than the cardiac catheterization and with rare exceptions it was also more rapid than during surgery. As indicated previously, one of the drawbacks of the method is the inability to obtain absolute pressure values. Artefacts were generally less troublesome than in the " P.C." tracings, because of less motion of the polyethylene tubing than the cardiac catheter.

Normal œsophageal balloon tracings have been described by Lasser and colleagues as being reflections of the left atrial pressure pulse. As in the other curves with which we are dealing, we have found considerable variation even in normal patients. A, C, and V waves may be identified, as in Fig. 10, although they are usually not as well defined as in this figure and may be split.

As compared with the normal, œsophageal balloon tracings in mitral valve disease showed a higher amplitude but little qualitative difference. The resemblance to direct left atrial tracings was good (Fig. 2, 6, 7), although exceptions also occurred here. Preoperative œsophageal balloon tracings gave a better indication than " P.C." curves of the contour of the left atrial pulse subsequently obtained at operation.

Œsophageal balloon and left atrial tracings were obtained in all 30 patients in the study. In one patient, the rhythm changed from auricular fibrillation at the time the balloon tracing was taken to sinus rhythm at operation, so the curves could not be compared. Of the remaining 29, in 20 the balloon tracing resembled the left atrial tracing. On the other hand, in 20 cases in which both " P.C." and œsophageal balloon curves were available, they resembled each other in only six. The correspondence between balloon and atrial pressure pulses was more pronounced in auricular fibrillation, probably because the curves are less complex when that rhythm is present.

When the V wave was prominent in the direct left atrial tracing, this prominence was often, but not always, reflected in the œsophageal balloon tracing (Fig. 6 and 7). However, we have been unable to confirm the presence of characteristic œsophageal balloon tracings in mitral stenosis or mitral insufficiency. It is true that a prominent late systolic wave (V wave) and a tendency for the curve not to fall to the base line after the C wave are found more often in mitral insufficiency than in mitral stenosis. We obtained the best example of such a tracing (Fig. 10) in a patient who was operated upon elsewhere.* This patient was found at operation to have marked mitral insufficiency. In another case, previously mentioned, in whom very mild insufficiency was greatly aggravated by

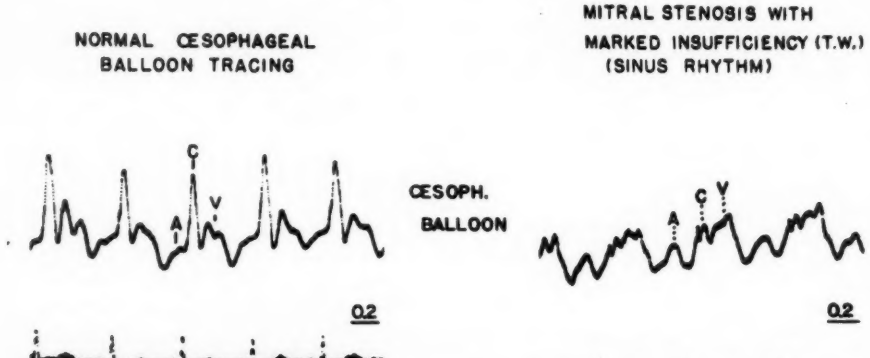

FIG. 10.—(A) Normal œsophageal balloon pulse tracing. (B) Tracing in a patient with proven mitral insufficiency and no stenosis. (Paper speed = 50 mm. per second.)

* We are indebted to Dr. Jere Lord, of the University Hospital, New York, for permission to study this case.

valvotomy, the post-operative œsophageal balloon tracing reflected to some extent the increased height of the V wave (Fig. 8). Unfortunately, the features mentioned above are not pathognomonic for mitral insufficiency, as they also occur in pure mitral stenosis, and are absent in an occasional patient with mitral insufficiency. In a given patient, therefore, the œsophageal balloon appears to have little or no value in the preoperative diagnosis of mitral insufficiency.

TABLE III

COMPARISON OF TIME BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN LEFT ATRIAL AND ŒSOPHAGEAL BALLOON TRACINGS*

	Left atrium		Œsophageal balloon	
	No. of cases	Average time (in seconds)	No. of cases	Average time in (seconds)
P to onset of A ..	9	0·06	9	0·07
P to peak of A ..	9	0·14	9	0·15
Q to onset of C ..	15	0·05	15	0·05
Q to peak of C ..	15	0·10	15	0·10
Q to onset of V ..	13	0·20	15	0·17
Q to peak of V ..	13	0·33	15	0·23

* No correction made for time of passage of pulse wave through catheter or polythene tubing.

In a group of cases in which accurate measurement was possible (Tables II and III) the time of inscription of the A and C waves relative to the electrocardiogram was the same in the œsophageal balloon as in the direct left atrial tracings. The V wave occurred slightly earlier in the former, possibly because of the more rapid heart rate.

SUMMARY

Direct left atrial, " pulmonary capillary ", and œsophageal balloon pressure pulses were recorded in a series of 30 patients operated upon for mitral stenosis. The purpose of the study was to determine how closely the " P.C." and œsophageal balloon tracings reflected those obtained directly from the atrium, and to estimate their value in the diagnosis of mitral insufficiency.

Of 27 patients who had pre-operative cardiac catheterization, " P.C." curves could be obtained in only 19. In all 30 patients satisfactory œsophageal balloon curves were obtained preoperatively and good left atrial tracings were recorded at operation.

With some exceptions, there was good correspondence among the three types of pressure curves recorded in a given case. However, there were many artefacts in both the " P.C." and œsophageal balloon tracings, which impaired their value.

In cases with pure mitral stenosis and sinus rhythm, the tracings showed no qualitative difference from the normal, but the pressure level was much higher. Auricular fibrillation gave rise to a plateau type of tracing beginning with the C wave and ending with the V wave.

Five of the 30 patients proved at operation to have mitral incompetence. Three developed this lesion after the valve was split.

Mitral insufficiency, either alone or in combination with mitral stenosis, tended to augment the V wave and prevent much of the pressure fall after the C wave. Changes of this character were unimpressive in the presence of auricular fibrillation, did not occur in every case of mitral insufficiency in sinus rhythm, and occasionally were present in what appeared to be pure mitral stenosis.

It was concluded that direct left atrial, " pulmonary capillary ", and œsophageal balloon pressure pulses could not be relied upon to diagnose mitral insufficiency when mitral stenosis was also present.

The authors are grateful to Dr. Richard P. Lasser for his advice in the construction and use of the œsophageal balloon, and to Drs. Lasser, Howard L. Moscovitz, and Samuel O. Sapin, members of the Cardiac Catheterization Team at The Mount Sinai Hospital, who assisted in much of the work.

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CHRONIC GENERALIZED MYOCARDIAL ISCHÆMIA WITH ADVANCED CORONARY ARTERY DISEASE

BY

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A disparity often exists between the extent of myocardial damage and the severity of the underlying coronary artery disease. Only where pathological examination has been supplemented by detailed injection studies is it possible to provide satisfactory interpretation of the changes found. From such studies the importance of collateral blood supply through enlarged anastomotic channels within the heart has become better appreciated in recent years.

Obliterative disease of the major coronary arteries, together with secondary changes in the smaller vessels, may result in the original coronary tree becoming distorted in a great variety of ways. Nevertheless certain basic trends in anastomotic development may be recognized. When the arterial changes are widespread and of extreme degree a characteristic vascular pattern and pathological picture may appear.

From an investigation of coronary artery disease, using a technique that included stereo-arteriography, four closely similar cases have been selected for presentation. These cases illustrate the extensive nature of the vascular changes that may be found in the subendocardial plexus of the left ventricle. No reference to the importance of this plexus in disease has so far been found in previous records; nor does the characteristic vascular pattern now to be described appear to have been mentioned hitherto.

The clinical and pathological findings broadly correspond to the features described in " acute coronary insufficiency " (Friedberg and Horn, 1939). The characteristic vascular pattern found in these cases is considered in relation to the distribution of focal necrotic lesions in the inner layers of the left ventricle, and also in relation to the freedom from massive myocardial infarction, notwithstanding severe obliterative coronary artery disease.

Material and Methods

The four cases to be presented are part of a series of 26 cases of advanced coronary artery disease which have been investigated post-mortem by a special technique. Thirty-six controls were examined of which 18 were patients with cardiac disease other than coronary artery disease; the remainder were cases without cardiac abnormality or with only minor departures from normality.

Each case was subjected to an analysis that included injection of the coronary arteries with a radio-opaque medium, followed by stereo-radiography of the intact heart and of the partially dissected heart. It is intended to publish the details of the method, but for the purpose of this presentation it may be pointed out that certain features of the technique were important in revealing

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the changes described and in making their demonstration readily recordable. These features included (*a*) a special modification of radiography which eliminated soft-tissue shadow; (*b*) a method of partial dissection of the heart, incorporating the use of cross-sections of the ventricles, both for radiography and for inspection; and (*c*) the emphasis placed on stereoscopy of all arteriograms. A few points in technique are discussed in more detail below because of their particular relevance to the demonstration of the changes found.

(1) The injection of bismuth-gelatin was made under controlled pressure. A standard pressure of 150 mm. Hg was used for the greater part of the series, including the third and fourth cases presented in this communication. The first two cases, however, occurred early in the investigation before the technique was completely standardized. In the first, a pressure of 180 mm. Hg was used and in the second 200 mm. Hg for part of the injection. It is felt that this increase in pressure has had no important influence on the findings.

(*a*) Other cases early in the series were subjected to the same order of pressure and did not show the changes found in these two cases.
(*b*) The second case in which the vascular changes were least was subjected to the highest pressure.
(*c*) The changes in the two later cases were essentially similar to the changes found in the first two.
(*d*) There was no evidence in the arteriograms or in the microscopic preparations of artefact distension of vessels.
(*e*) Other workers have used pressure ranges of the same order, and higher, without reporting risk of damage to vessel walls and without describing the same features.

(2) The myocardium was sliced at intervals to form transverse sections of both ventricles. In this way the distribution of changes was readily appreciated. The naked-eye appearances were confirmed by multiple histological sections. These included the entire circle of the left ventricle, and most of the right, at a representative level approximately half-way between the atrioventricular groove and the apex. It is on the basis of these sections stained with hæmatoxylin and eosin and by Verhoeff—or Weigert—and van Gieson methods that the diagrams of the distribution of ischæmic changes are drawn.

(3) Measurements of coronary ostia were made by the gentle insertion of curved glass probes of graded size prior to the introduction of the cannulæ.

(4) The heart weights quoted have had 30 g. subtracted from the recorded weights in order to make correction for the added weight of bismuth-gelatin mass.

(5) Red and blue pigments were incorporated in the medium before injection into the right and left coronary arteries respectively.

Case Reports

Case 1. A. MacD., a woman aged 67 years. Civil servant. No. 315/52. A single woman of middle height and moderate obesity, she had suffered from angina of effort for thirteen years, during which there was progressive increase in the frequency and severity of attacks. Although at times there were temporary episodes of increased severity, the general course was unremittent. Five years before death, cervical sympathectomy was performed with some temporary reduction in the severity of the pain but not of the disability. Death was due to mediastinitis following the removal of a carcinoma of the thyroid. On one occasion only did the duration of an anginal attack last longer than thirty minutes and that was nine years before her death. Despite numerous severe attacks of angina there was no instance in which myocardial infarction could be diagnosed with certainty on clinical or electrocardiographic grounds.

Findings at necropsy. The heart was enlarged as the result of left ventricular hypertrophy and gross increase of epicardial fat. There was no valvular abnormality, and no hypertension had been observed during the last few years of life.

The myocardium of the left ventricle showed widespread patchy fibrosis of the inner zone of the

entire left ventricle. There was no naked-eye evidence of recent infarction, but scanty areas of focal necrosis were found on histological examination, likewise in inner zonal distribution.

The coronary arteries showed gross atherosclerotic disease with severe narrowing of two, and occlusion of one, main branch. In addition, atherosclerosis of the aorta was accompanied by severe narrowing of both coronary ostia. Large-scale superficial anastomoses formed communications between the epicardial vessels, but the greatest degree of anastomotic development was found in the inner zone of the entire left ventricle. That this zone of vascularity was indeed a dense network of anastomotic channels was demonstrated by stereoradiography; and that filling took place from both coronary vessels was confirmed by the intimate intermingling of pigments in all channels.

Case 2. J. E., a man aged 68 years. Retired excess luggage clerk. For twelve years this man suffered from relentlessly progressive, severe angina, provoked by slight exertion. The onset of the illness was heralded by pain which lasted for one hour and was accompanied by sweating and vomiting. There was a second episode of enduring pain five years later. For three years before death pain had been occurring also at rest.

Increased severity and frequency of anginal attacks in the terminal six months culminated in fatal " status anginosus ". Multiple electrocardiograms had been taken over a period of years, and until two days before death there had been no record that suggested myocardial infarction. This last record suggested anteroseptal infarction, which was not, however, confirmed at necropsy.

Although the blood pressure recorded during life was of the order of 200/100, the heart showed no enlargement. The myocardium showed inner zonal fibrosis of the left ventricle and a few scattered areas of focal necrosis. An advanced degree of coronary artery disease was present, with severe narrowing of the right coronary and left circumflex arteries, together with stenosis of both coronary ostia. At no point was there evidence of recent change in the coronary arteries; there was no recent occlusion or intimal hæmorrhage. Increase in the arterial channels was noted in the deeper layers of the left ventricle, with increased prominence of anastomoses in this area as well as elsewhere in the heart.

Case 3. B. M. was a married woman of 73 years, of small build and poor nutrition. There had been progressively increasing effort pain over a period of ten years with angina also at rest for the last two years. Except terminally, attacks of pain were always of short duration and were relieved by rest or trinitrin.

Four weeks before death there was enduring pain which recurred two weeks later with greater severity, and she was admitted to hospital in shock as the result of recent myocardial infarction. Electrocardiograms suggested that this was anteroseptal in distribution. Her condition deteriorated and she died two weeks after admission.

At necropsy widespread atherosclerosis was found. There were cerebrovascular changes; carcinoma of the stomach, without metastasis, was an incidental finding. The heart was enlarged only as the result of fat, and was the seat of advanced coronary disease. In addition both coronary ostia were stenosed. There was highly developed inter-arterial anastomosis, affecting all areas but with greatest intensity in the deep zone of the entire left ventricle. The " inner shell " of the left ventricle showed speckled infarction, composed of small focal areas of necrosis, none larger than 3 mm. in diameter. Fibrosis was also found in the same zone. The outer and subendocardial layers were not involved in the acute changes. No direct precipitating cause for infarction was found; in particular there was no recent occlusion of a coronary vessel. The terminal episodes were of the nature of acute coronary insufficiency.

Case 4. J. S. A housewife, aged 70, had suffered from anginal pain on slight effort for ten years. By keeping within her limits distressing pain was avoided and episodes never lasted longer than ten minutes. At no time was there clinical evidence of infarction except terminally. In latter months the condition was more severe. She was known to have suffered from hypertension for at least two years, with a blood pressure of 200/140 mm. Hg. Nineteen hours before her death she developed severe enduring sternal pain requiring morphine for its relief, and she was admitted to hospital in a state of shock.

At necropsy severe atherosclerosis of the aorta and coronary arteries was found. The heart was enlarged mainly from left ventricular hypertrophy and on section a zone of infarction was seen to encircle the inner half of the entire left ventricle. The appearances were consistent with an infarct of less than twenty-four hours' duration and which was composed of multiple focal areas. The coronary arteries showed no acute changes, in particular no recent occlusion, to account for the development of infarction; but they were the seat of gross atherosclerotic disease and both coronary ostia were stenosed.

Summary of Findings in the Four Cases

A close similarity was found both in positive and negative findings in these four cases, and some of the features are summarized in Tables I and II.

TABLE I

Clinical Features of Four Patients with Prolonged Progressive Myocardial Ischæmia

Case number	1	2	3	4
Age	67	65	73	70
Sex	F	M	F	F
Parity	0+0	—	0+0	7+1
Duration of history (years)	13½	12½	10	10+
Usual duration of attack (minutes)	2–3	2–3	" A few "	10
Frequency	20/day	19/day	" Daily "	" Frequent "
Longest attack apart from terminal episode	30 min.	60 min.	" Always short "	10 min.

TABLE II

Pathological Features of the Coronary Arteries in Four Patients with Progressive Myocardial Ischæmia

Case Number	1	2	3	4
Age in years	67	65	73	70
Sex	F	M	F	F
Anatomical " balance "	R=L	L+	R+	R+
Ostial diameter (mm)—				
Right	1·5	1	1	1·5
Left	2	2	2	2
Occlusions—				
Recent	—	—	—	—
Old-standing, complete	—	1	—	1
Old-standing, recanalized	5	3	5	2

In each case there was a long history of effort pain, and in two pain occurred latterly also at rest. Although angina was severe in three cases, it is felt that the significant feature in this group was not so much the severity of the pain but the relentlessly progressive course, uninterrupted by remissions, and of long duration. Exacerbations occurred but clinically recognized episodes of myocardial infarction were absent except as a terminal event.

In each case there was advanced coronary disease and, in addition, there was also narrowing of both coronary ostia. The blood Wassermann reaction had been negative in life and no evidence was found post mortem of syphilitic involvement of the aorta.

Distributed between the four cases there were two instances of complete occlusion of a main

arterial stem and fifteen of severe narrowing (i.e. less than 1 mm. in diameter). Detailed investigation suggested that the latter represented recanalization of old occlusions. There was no instance of recent occlusion.

In no case was there evidence of recent or old-standing massive myocardial infarction in the territories of narrowed or occluded arteries. On the other hand, recent myocardial damage could be recognized on gross examination in two cases, and was in the form of multiple focal areas of necrosis measuring 1–3 mm. in diameter, which in aggregate formed a ring of infarction as seen in cross-section throughout the inner shell of the left ventricle. The immediately subendocardial layer was not affected. In the other two cases, isolated areas of focal necrosis in inner zonal distribution were found on histological examination. In no case were these changes the result of recent occlusion.

Fibrosis was of diffuse patchy type and probably represented previous episodes of focal necrosis. It was mainly confined to the inner zone of the left ventricle and likewise spared the immediately sub-endocardial layer. The distribution of focal necrosis and fibrosis in the four cases is shown in Fig. 1. A section through the interventricular septum of Case 4 is shown in Fig. 7 in order to demonstrate the coincidence of vascular and fibrotic changes in the same picture.

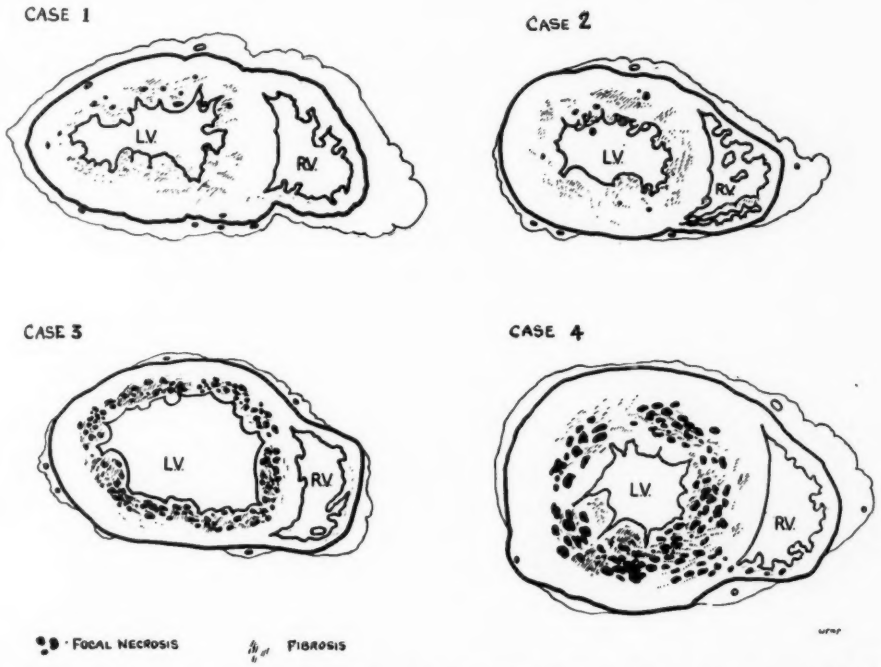

FIG. 1.—Diagram of transverse sections through the ventricles, showing the distribution of recent and old-standing myocardial damage.

No immediate precipitating factor for the development of necrosis was found. Only in the first case was death directly attributable so far as is known to a factor other than coronary disease, although in the third case cerebrovascular disease and the debilitating effects of gastric carcinoma doubtless had some influence.

Intimal hæmorrhages occurred in two of the cases but without apparently having caused significant narrowing of the lumen. All were intramural in position and of small size, and their presence was unaccompanied by thrombosis. In no case was there valvular disease or congenital abnormality.

Description of the Vascular Pattern in Chronic Generalized Myocardial Ischæmia

The characteristic vascular change that was found in the four cases described is shown in Fig. 2. In this radiograph of an intact injected heart, the " vascular density " in the central area of the left ventricle forms a striking contrast to the pattern seen in a slightly enlarged but otherwise normal heart (Fig. 3). When the paired arteriograms from the abnormal cases were viewed stereoscopically it was seen that the dense central area was composed of a network of dilated inter-communicating channels which occupied the entire inner zone of the left ventricle.

The position of this network may be demonstrated in two dimensions by taking transverse sections through the ventricles (Fig. 4 and 5). In these the contrast of the distribution of arterial vascularity in the presence of disease to the condition found in health may be appreciated by comparison with the section of a normal heart (Fig. 6). The distribution of the vascular changes will later be correlated with the myocardial findings.

As might be expected, dilated anastomoses were also found on the surface of the heart. These were situated at many areas but were especially large in the neighbourhood of the apex and in the atrio-ventricular groove. These are common sites for anastomoses to be found in the presence of coronary artery disease.

In circumstances where all major branches of the coronary arteries have been affected by atherosclerotic disease of the severity and chronicity found in these cases, and where widespread dilatation of anastomoses has likewise reached an extreme degree, it is evident that all semblance to the original coronary " tree " has been lost. The tree has been replaced by a network.

When this stage has been reached the main coronary arteries have lost most of the local importance formerly held by them in regard to the blood supply of their individual territories, and occlusion of major branches can occur, as in the cases reported, without the development of local myocardial infarction. Indeed, it may be that once the coronary circulation has been converted into such a network, regional (as opposed to zonal) myocardial infarction becomes anatomically impossible. On the other hand, every obstruction to a main vessel presumably introduces further resistance to total flow through the coronary network, and it is possible that some of the exacerbations that occurred in the clinical courses of the patients described were brought about in this way.

In all grades short of that producing myocardial infarction, ischæmia appears to promote the dilatation of the smaller coronary vessels, including the interarterial communications. The flow of blood from a relatively well provided area to the territory of an artery that has become narrowed may be assisted by the vasodilatation that takes place under the influence of anoxia (Gregg, 1950). Moreover, increased blood flow itself has evidently a dynamic influence on enlargement of arteries.

Myocardial ischæmia of a degree insufficient to cause massive structural damage may yet act as a potent stimulus to anastomotic enlargement, provided that it is operative for a sufficiently long period of time. In the cases reported the long histories of anginal pain bear witness to the duration and severity of myocardial ischæmia. The finding that both coronary ostia were narrowed in all cases, and in addition that all major coronary arteries were extensively diseased, suggests that myocardial ischæmia must inevitably have been generalized. All the pathological findings are in keeping with this concept of chronic generalized myocardial ischæmia.

It is submitted that the conversion of the coronary tree into an arterial network provided the anatomical basis upon which structural myocardial damage was largely prevented or delayed, and

FIG. 2.—Arteriogram of the entire heart, showing the characteristic vascular pattern found in chronic generalized myocardial ischæmia. Case 4.

FIG. 3.—Arteriogram of the entire heart, showing normal appearances in a control case.

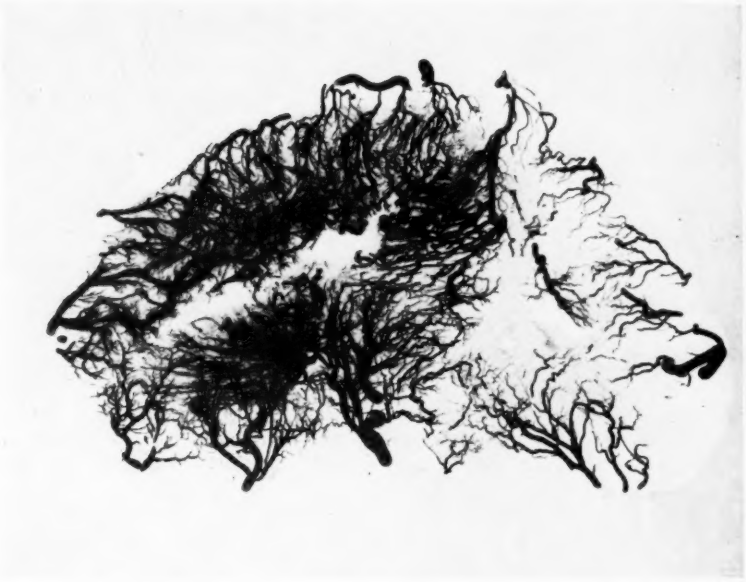

FIG. 4.—Arteriogram of transverse section through the ventricles. Case 1.

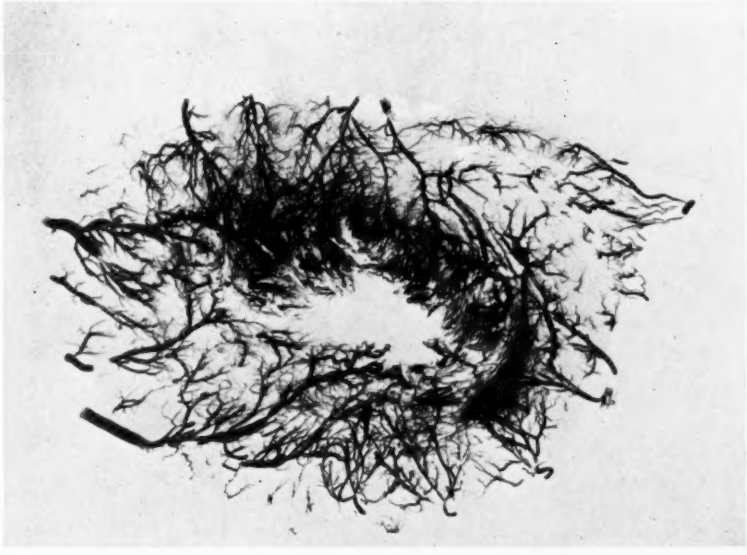

FIG. 5.—Arteriogram of transverse section through the ventricles. Case 4.

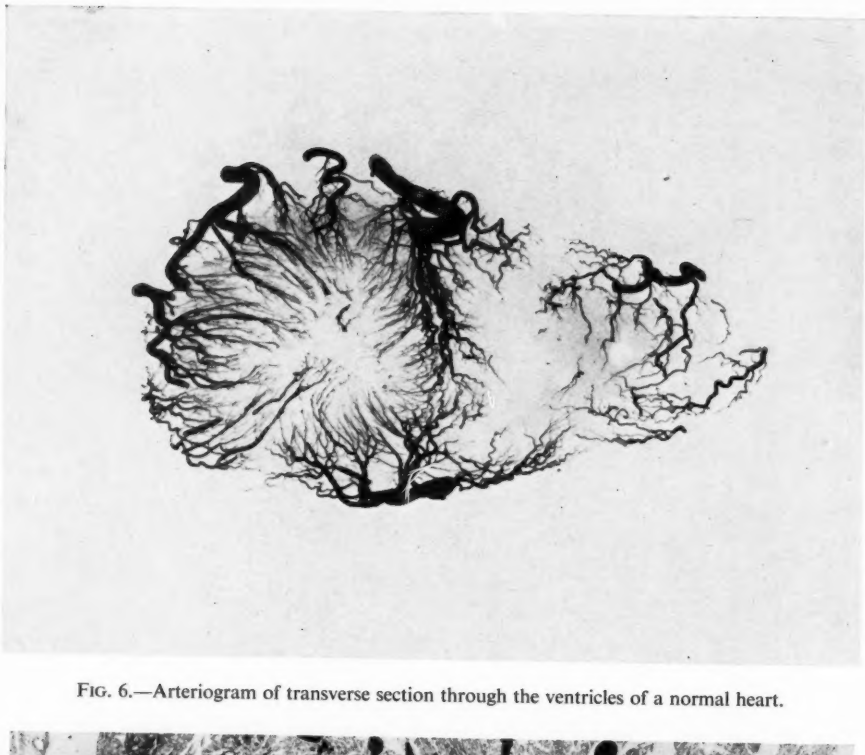

FIG. 6.—Arteriogram of transverse section through the ventricles of a normal heart.

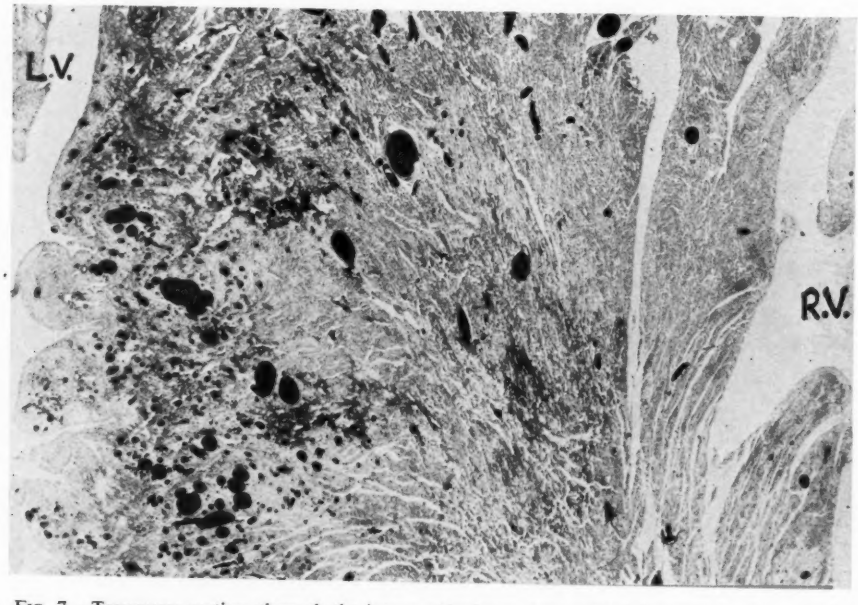

FIG. 7.—Transverse section through the interventricular septum stained by van Gieson's method. Fibrosis is seen mainly on the left ventricular side of the septum. The injection medium within the arteries appears black. Case 4.

which conditioned the focal character and inner-zonal distribution of myocardial necrosis when it occurred. These last points will now be considered in more detail.

Regional or Zonal Myocardial Infarction

The myocardial damage that results from ischæmia may be regarded as falling into two main types according to the manner in which the lesions are distributed. In their typical forms these two types of myocardial infarction can be readily distinguished but intermediate forms exist which are less clearly defined. The distinction between regional and zonal myocardial infarction is a useful one, for, as will be seen, the distribution of the lesions is closely related to the underlying changes in the coronary circulation.

Regional Myocardial Infarction. In many cases of coronary artery disease the obliterative changes fall mainly on one major artery. When myocardial infarction follows the occlusion of this artery, the myocardial damage is restricted to the territory of the affected vessel. The extent of the damage within that region may, however, vary from massive " through and through " infarction of almost the entire anatomical territory to slight damage in the form of a few small areas of necrosis. These small areas of damage tend to be restricted to the deeper layers of the left ventricle. These points are well established and are illustrated in Fig. 8, A and B. A factor that largely determines the extent of myocardial damage resulting from a particular occlusion is the state of the collateral circulation to the affected area that is immediately available at the time of occlusion.

Inner Zonal or " Sub-endocardial " Infarction. The occurrence of multiple focal areas of necrosis in ischæmic heart disease is likewise well recognized and its association with the clinical conditions of " acute coronary insufficiency " has been pointed out by Büchner (1939) and by Friedberg and Horn (1939), Master *et al.* (1941) and Horn *et al.* (1950). These observers recognize that the focal ischæmic lesions are distributed predominantly to the deeper layers of the muscle of the left ventricle. The present series is in entire agreement with their findings. On the other hand, in the published cases of acute coronary insufficiency which have been quoted, injection techniques were not employed in the examination of the coronary arteries. Accordingly, no correlation with the vascular pattern could be made. Further, no published description of the vascular pattern found in the present series has been discovered. As already indicated, this vascular pattern is felt to be the key to the other pathological changes.

The Relationship Between Anastomoses and the Relief of Ischæmia

It has been stated by Zoll *et al.* (1951) that the development of increased arterial anastomosis in the coronary circulation is a compensatory change, which indeed it is. It may be argued, however, that the beneficial effects of anastomotic development are fundamentally fortuitous; and that the favourable outcome that may result from anastomotic enlargement bears no causal relationship to the processes conditioning that enlargement. This point is made in connection with the four cases under presentation, because they provide clear demonstration that vascular " adaptations " in the form of dilated anastomoses occur as a secondary effect of ischæmia, and that these changes take place quite independently of the capacity of the " friendly neighbouring arteries ", as Herrick called them, to provide relief (Herrick, 1912). Indeed, in the present investigation the greatest complexity of anastomotic development has been found in those hearts in which enlargement of communicating vessels has failed to relieve ischæmia; where, so to speak, each artery has been so compromised by disease that it can barely carry sufficient blood for the basic needs of its own territory, and is therefore not in a condition to afford charity for its neighbours. In these circumstances, where inflow of blood to the whole organ has been reduced at source, internal rearrangement of channels of supply can at the best achieve only a more uniform distribution of poverty. This appears to have been the situation in the four cases described. It is understandable

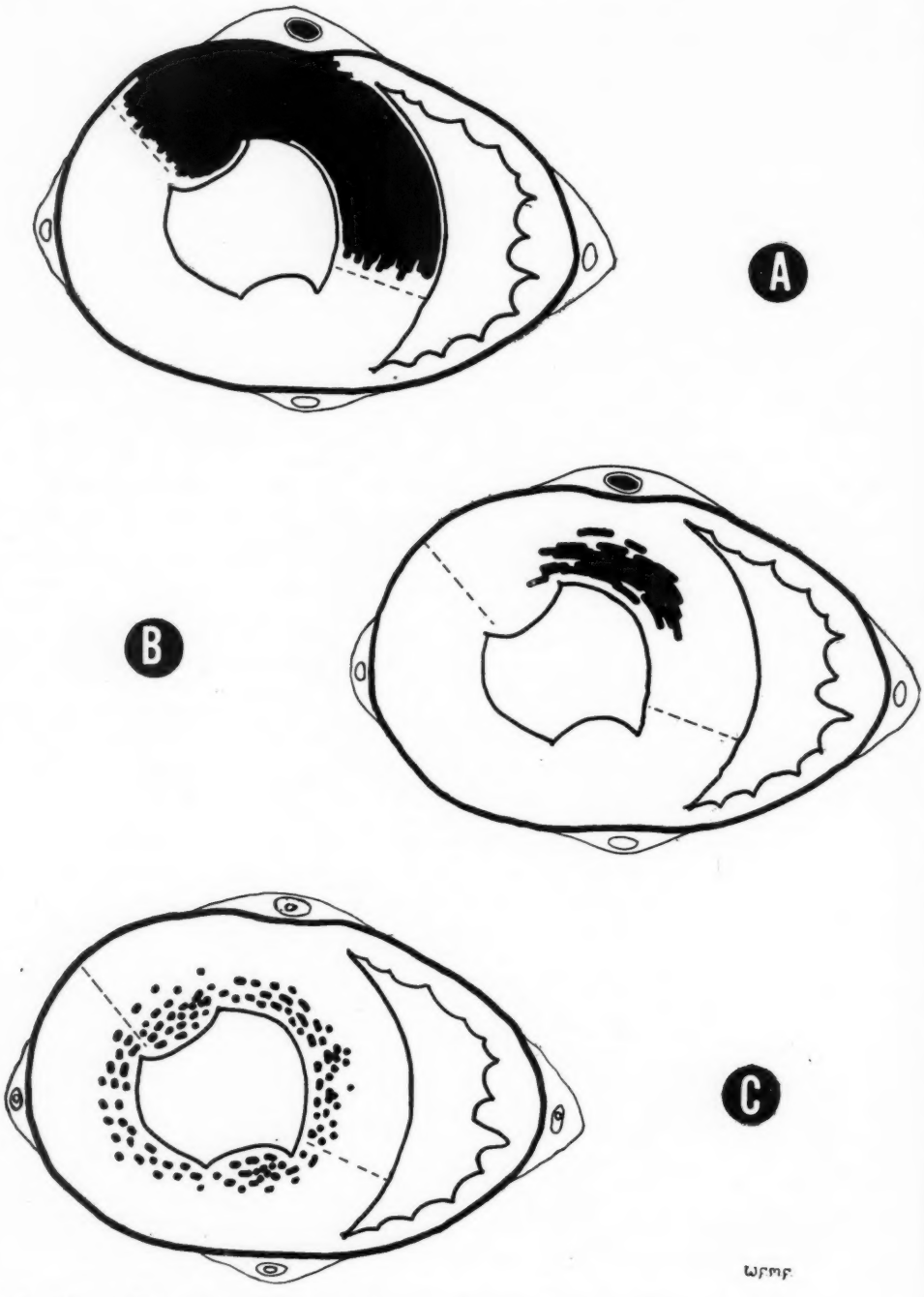

FIG. 8.—Diagram illustrating the distribution of damage in regional and zonal infarction. (A) Regional infarction, massive, " through and through ". (B) Regional infarction, sub-total. (C) Inner zonal, " ring " infarction (focal necrosis).

that in such circumstances the least favourably situated areas should have suffered first, and that these should have lain farthest from the source of blood supply; and moreover should have lain in those layers of the left ventricle to which delivery of blood during systole is impeded to the greatest extent by extravascular compression.

Factors Influencing the Inner Zonal Distribution of Focal Necrosis

The most obvious factor conditioning the inner zonal distribution of focal necrosis in acute coronary insufficiency is one of distance from supply. This was the explanation which first appealed to Friedberg and Horn (1939). The demonstration of the conversion of the coronary " tree " into a network of the order that has been revealed in this investigation puts this explanation on a sound anatomical basis.

Other explanations have been put forward and mention is made of two of them. From the observation of Johnson and Di Palma (1939) that a gradient of pressure exists during systole which diminishes from the inner to the outer layers of the left ventricle, it was deduced (Horn *et al.*, 1950) that the inner layers are therefore more susceptible to oxygen deprivation. These authors also offer in explanation the evidence derived from acute experiments on the dog in which it was observed that the sub-endocardial layer of the left ventricle seemed to have a poorer collateral circulation than the epicardial portions (Prinzmetal *et al.*, 1948). It is felt that such evidence cannot be directly applicable to the human heart in the presence of advanced coronary artery disease. In this connection it may be observed that of the manifestations of coronary artery disease, " acute " coronary insufficiency may well have the most chronic pathological basis.

It is quite possible that the vascular pattern described in this presentation is present in at least the majority of cases of acute coronary insufficiency, when this condition is primarily the result of advanced coronary artery disease, and that this vascular pattern in turn conditions the nature of the clinico-pathological syndrome. The small size of this series, the absence of previous descriptions of the vascular pattern, and the lack of evidence in regard to the smaller vessels in the reported cases of acute coronary insufficiency, prevent certainty on this point.

Summary and Conclusions

A series of 26 cases of advanced coronary artery disease with 36 controls were investigated after death by a technique that included stereo-arteriography.

Four cases were selected for special description: they had in common a long history of relentlessly progressive anginal pain, widespread severe coronary artery disease, narrowing of both coronary ostia, inner-zonal distribution of ischæmic changes in the left ventricle, and a characteristic pattern of adaptation of the smaller vessels of the coronary circulation.

Anastomotic development was of an advanced degree and affected the sub-endocardial arterial plexus of the left ventricle with special emphasis.

Terminal myocardial damage was in the form of focal necrosis, which was extensive in two cases, and which was in no case precipitated by recent coronary artery occlusion. Fibrosis in the same distribution was thought to be the sequel of earlier episodes of focal necrosis. The pathological findings were consistent with the features described in acute coronary insufficiency. Despite evidence that thrombotic occlusion had been of frequent occurrence, there was no definite regional infarction. It is postulated that the conversion of the coronary circulation into a network of dilated channels had removed the anatomical basis upon which regional infarction could have occurred.

Factors determining the distribution of focal necrosis to the inner layers of the entire left ventricle are discussed and it is suggested that remoteness from arterial supply is the most likely single factor governing this distribution.

Attention is drawn to the very chronic nature of the background of arterial disease which was found in these cases in which coronary insufficiency was primarily due to coronary atherosclerosis.

Little reference has been found to the importance in disease of the sub-endocardial plexus; and it is believed that the vascular pattern observed in the four cases presented has not previously been described.

The cases reported had all been under clinical observation in the wards of the Cardiological Department of the Royal Infirmary, Edinburgh, under Dr. A. Rae Gilchrist to whom I am indebted for his encouragement and advice. The pathological investigation was undertaken in the Pathology Department of the Royal Infirmary and University of Edinburgh; and to Professor A. Murray Drennan and Dr. R. F. Ogilvie I am deeply grateful for the facilities provided and for their stimulating and critical guidance. The photographic reproductions were carried out in the Department of Photomicrography under Mr. T. Dodds, and facilities for radiography were afforded by Professor J. C. Brash in the Department of Anatomy.

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THE DIAGNOSIS OF CONGENITAL HEART DISEASE IN INFANTS BY CATHETERIZATION AND SELECTIVE ANGIOCARDIOGRAPHY

BY

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The anæsthetic and surgical techniques are now so highly developed that it is possible to operate on congenital heart disease even in infants. This is important progress, as about half the children with congenital malformations of the heart die before the age of one year: 30–40 per cent of these suffer from conditions that can theoretically be corrected by operation with the possibilities that now exist—a percentage that will probably increase in the years to come. It is thus an urgent task to try to diagnose these malformations as early as possible as surgical correction is frequently necessary and may be accomplished safely and successfully in this age group.

A prerequisite for surgical treatment is an accurate diagnosis. The diagnostic methods are clinical, heart catheterization, and angiocardiography. The routine clinical diagnosis consists of case history, auscultation, electrocardiography, rœntgen examination, etc. Assisted by these simple means it is often possible to make a diagnosis correct enough for a decision whether the malformation can be treated by surgery or not, and whether this is desirable. In older children with congenital heart disease about two-thirds have such characteristic clinical findings that a comparatively satisfactory diagnosis can be made, for instance, with persistent patent ductus arteriosus, coarctation of the aorta, the tetralogy of Fallot. It is, however, necessary in a number of patients to use more complicated methods, heart catheterization and angiocardiography, which have proved of very great value for a correct anatomical and functional knowledge of the nature of congenital malformations of the heart and their influence on the circulation.

The younger the children with congenital heart diseases, the more difficult it is to make a relatively sure diagnosis on clinical findings alone. This is partly because there are far more types represented in the younger age group, viz., those serious conditions in which the children die early. The incidence of combined lesions is high and often accounts for the serious difficulties in early life. Besides, the general X-ray examination is not of the same value in infants as in later years, and the X-ray appearance of the heart and the great vessels in different heart lesions is often not characteristic at this age. Fluoroscopy is difficult because of the crying and lack of co-operation by the child, because of the physiological tachycardia, and because the thymus often overlaps the base of the heart and the great vessels.

The size of the heart is in our opinion of value in the diagnosis, and the rœntgenological determination of the heart volume is the most accurate method available. The cardiothoracic ratio, still widely in use, is unreliable (Lind, 1950). A heart that is large enough to suggest a doubtful prognosis is a main indication for investigation in acyanotic congenital lesions. The lack of differential criteria in the exact diagnosis of the cardiac malformation in infants with large hearts and evidence of increased blood flow to the lungs is well known. Therefore, in order to make a correct diagnosis in infants, heart catheterization and angiocardiography have to be applied in most cases of malformation of the heart. Till now, the examinations have been concentrated mainly on older children, i.e. from about 3–4 years of age, and adults, mainly because there are greater technical difficulties in using these complicated methods in infants than later in life. Later experiences,

however, have shown that these methods can well be applied on infants (Ziegler, 1954) and it is, therefore, now an important pædiatric problem to get a clear picture of the value and possibilities of these methods of examination in this age group.

Technique of Examination

Anæsthesia. Our examinations have been performed under full or partial anæsthesia. In most cases narcodorm (the sodium salt of β-bromallyl-isopropyl-N-methyl-barbituracid) is used rectally, whereby the suitable dose in the end seems to be about 2·5–3 cg. per kg. body weight from a 5 per cent solution, given in an equal volume of water. If required during the examination small intravenous injections can be added through the inserted catheter. In addition, local anæsthesia is used.

Narcodorm has, like all barbiturates, a distinct and unpleasant depressing effect on the respiration that in three of our cases has caused a temporary interruption of the respiration, so that the patients for a short time have been given artificial respiration without this stopping the planned course of the examination. All three were given 3·5–5 cg. of narcodorm per kg. body weight: after having reduced this dose to 2·5–3 cg. per kg. we saw no symptoms of cessation of respiration and the anæsthesia seemed to be adequate. In 14 of 33 patients examined who were given a maximum of 3 cg. narcodorm per kg., there had to be added 0·3–0·7 cg. per kg. body weight intravenously through the catheter just before angiocardiography. It should be possible to perform intubation immediately, if necessary, but we have never used it. The infants come to the examination on an empty stomach (no food for the last four hours) and a water enema is given three hours before the rectal anæsthesia.

In infants and small children catheterization is best done through the saphenous vein and the inferior vena cava rather than through an antecubital vein (Ziegler, 1954). We have administered no drugs such as pronestyl or quinidine prophylactically. The catheter is inserted into the vena saphena magna, although the femoral vein has been used in four cases, as the saphenous vein was too narrow. During the catheterization there was a permanent drip of a physiological saline solution without heparin through the catheter. Catheterization was tried in 51 infants, with success in 50 of them. In two cases the examination could not be performed because of the small size of the saphenous vein, but one of these has later been catheterized through vena saphena on the other side without difficulty.

It is advisable to have continuous electrocardiographic observations routinely during cardiac catheterization and angiocardiography. Extrasystoles and/or tachycardia (more than 225 beats a minute) are common and may force interruption of the examination (5 out of 50 cases). In 2 of these 5 cases paroxysmal ventricular tachycardia occurred and required withdrawal of the catheter to the vena cava and interruption of the examination and drug administration.

Angiocardiography. When the contrast medium has to be injected directly into the heart it is of vital importance that the catheters used are thin-walled enough. We have used the Lehmann catheter No. 5F, 6F, or 7F (United States Catheter Corporation, Glenn Falls, N.Y.; catheter No. 5F used 13 times, No. 6F 35 times, and No. 7F twice). The amount of contrast injected has been 1·1–1·9 ml. per kg. body weight—in half of the cases 1·5–1·6 ml. per kg. body weight. Generally we have used Rheopak Astra, 70 per cent.

To obtain the maximum of information from this form of angiocardiography, the injection should be made rapidly and finished before the contrast material reaches the left side of the heart. This passage of the contrast medium requires about 3–4 heart systoles. As the heart rate in infants during these examinations range between 180 and 220 beats a minute, that is about 3 beats a second, it means that the contrast medium should be injected within a second. This is only possible when using special syringes, operated either by hand via a lever or better, as has been done in these examinations, with the help of a syringe operated by compressed air (Gidlund). The pressure used for injection has been 5–6 kg./cm.^{2} The syringes in question are connected with the rœntgen apparatus in such a way that the exposures are automatically released when the injection is made.

It is also necessary to take the X-ray pictures with very short intervals and preferably in two projections. We have used a cassette changer, manufactured by Georg Schönander in Stockholm, that has a rate of 6 pictures a second during 5 seconds in two positions at right angles to each other (a total of 60 pictures in 5 seconds).

Examples are given in Figs. 1–6.

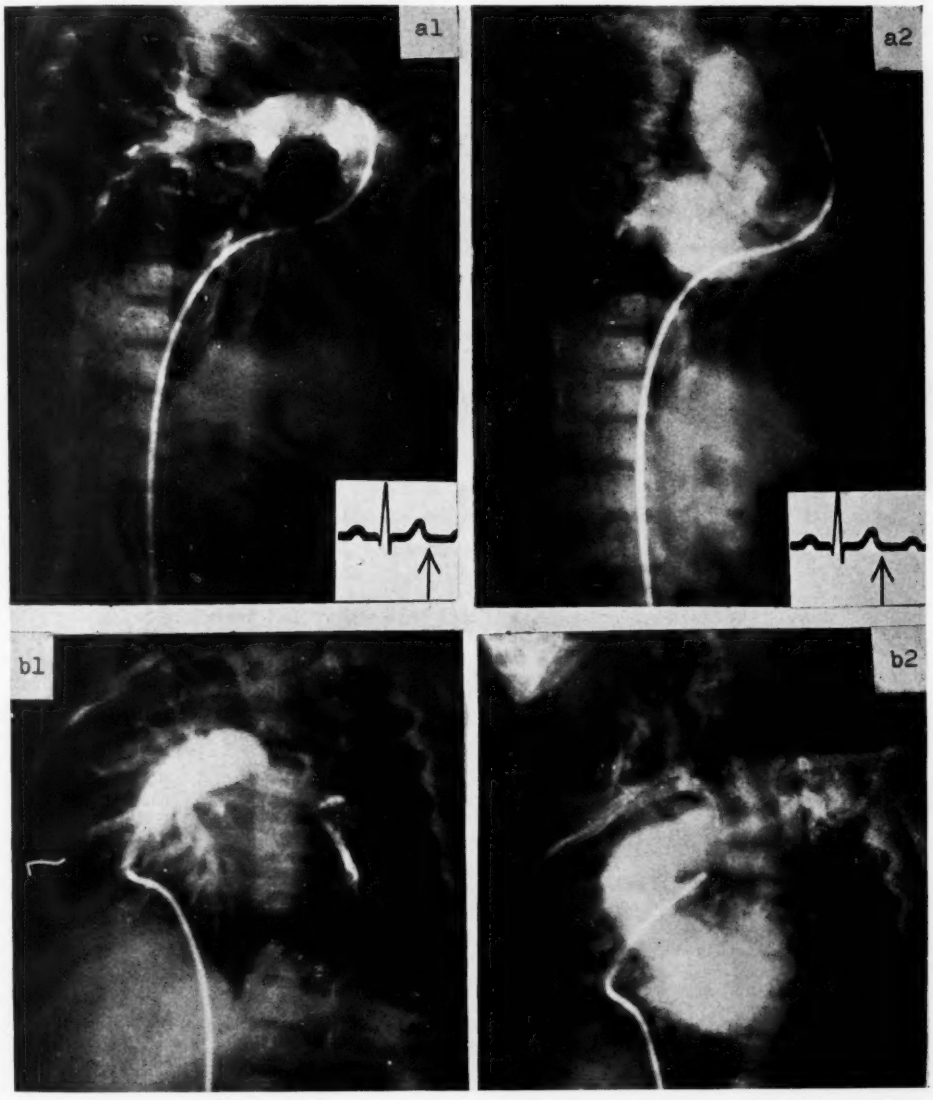

FIG. 1.—*Coarctation of the aorta.* Anterior oblique projections, right (a_1a_2), left (b_1b_2). Injection through a catheter into the pulmonary artery. (a_1b_1) The pulmonary artery is intensely opacified and shows a normal pattern. The pulmonic valves are clearly seen (a_1). (a_2b_2) The pulmonary circulation is completed 2·0 sec. later. Satisfactory opacification of the left side of the heart is seen. The ascending aorta is dilated. The length and degree of the narrowing of the coarcted area is clearly shown.

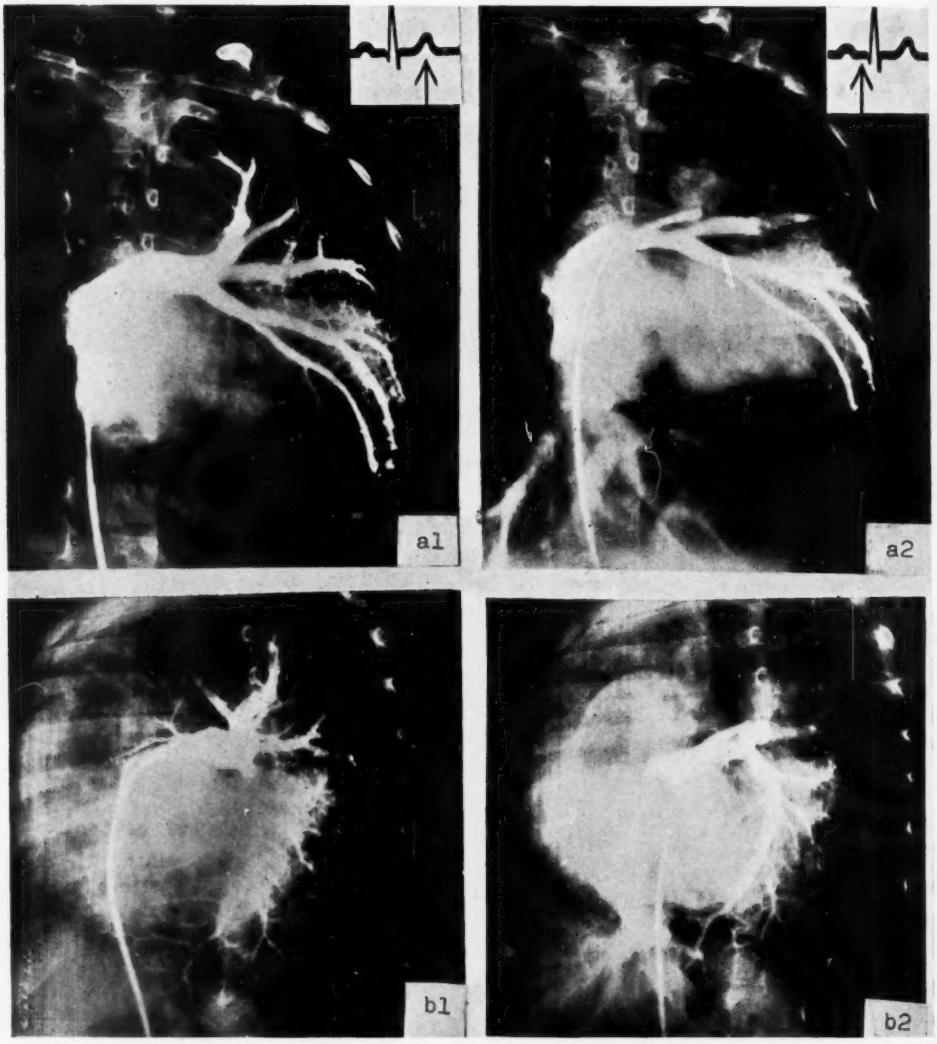

FIG. 2.—*Atrial septal defect with a left-to-right shunt.* Anterior oblique projections, right (a_1–a_2), left (b_1–b_2). Injection into the left atrium through a catheter. (a_1b_1) The left atrium in diastole is well opacified. Some contrast is already seen in the right atrium (b_1). There is intense retrograde filling of the left superior pulmonary vein. (a_2b_2) In the following atrial systole a large shunt into the right atrium is seen. The right atrium is opacified to the same extent as the left. Reflux occurs into the inferior vena cava.

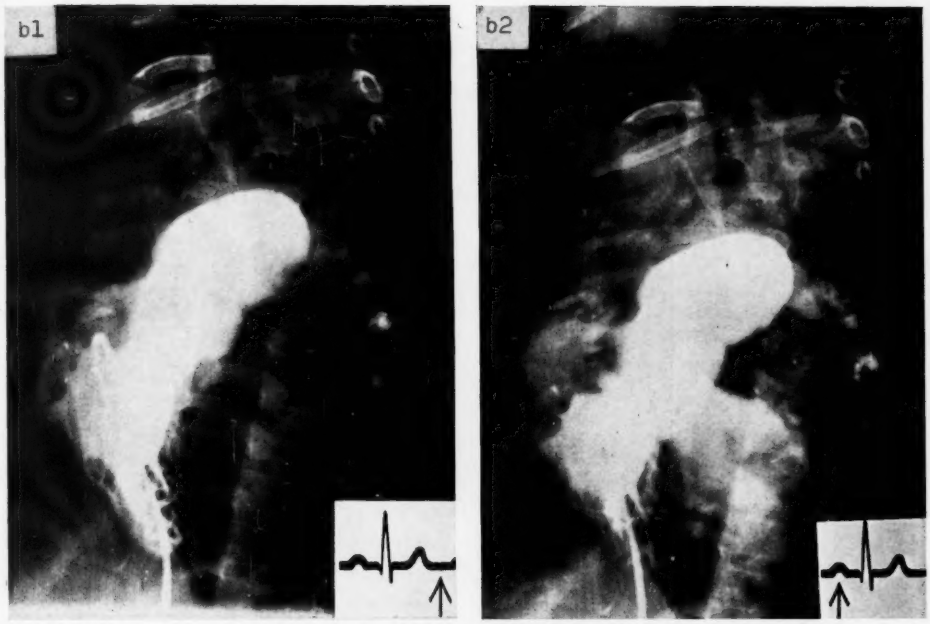

FIG. 3.—*Ventricular septal defect.* Left anterior oblique projection (b_1b_2). Injection into the right ventricle through a catheter. (b_1) The right ventricle and the pulmonary trunk are heavily contrast-filled. (b_2) At the end of the same ventricular diastole a right-to-left interventricular shunt is seen. The size of the defect can be roughly estimated.

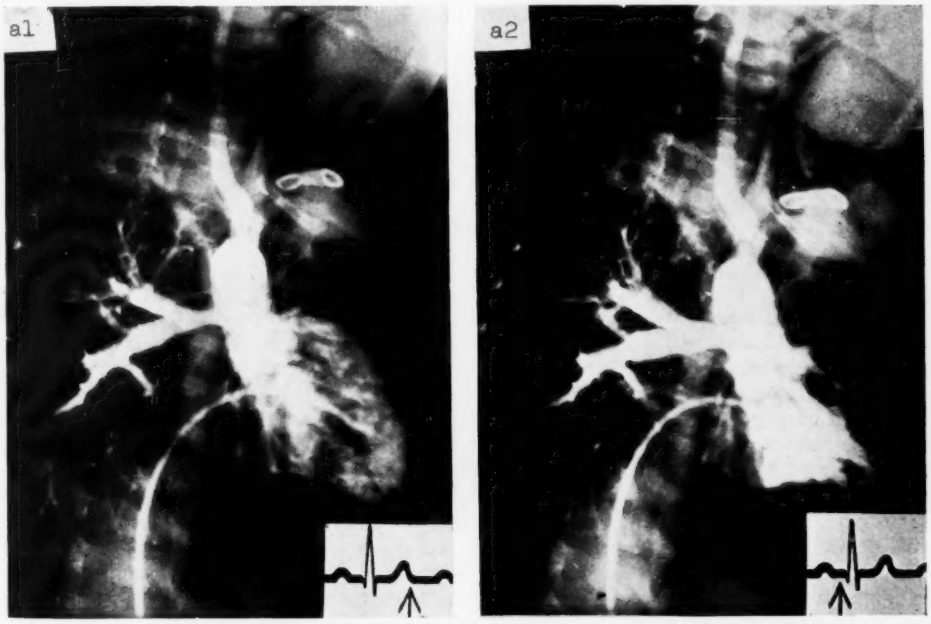

FIG. 4.—*Tetralogy of Fallot.* Right anterior oblique projections (a_1a_2). Injection through a catheter into the right ventricle. (a_1) The right ventricle is well filled with contrast. A broad aorta with an anteroposed origin is filled with contrast simultaneous with filling of the pulmonary artery. The infundibulum appears narrow and the main pulmonary artery is undersized. (a_2) The infundibulum during ventricular systole is visualized as a thread-like lumen. There is oligæmia of the peripheral lung fields. The pictures suggest that the infundibular stenosis is of functional significance only during ventricular systole.

FIG. 5.—*Transposition of the great vessels.* Right anterior oblique projection. Injection was performed through a catheter directly into the right ventricle. This heart chamber is heavily opacified and shows at its border an irregular pattern, due to increased trabeculation in right ventricular hypertrophy. The aorta originates from the right ventricle and the arch is widely bowed. The coronary arteries are also visualized. No right-to-left interventricular shunt is seen. In the "aortic window" numerous fine vessels characteristic of bronchial collaterals can be seen.

PATIENTS EXAMINED

At Dronning Louises Børnehospital, Copenhagen, infants with congenital malformations of the heart have been examined by means of simultaneous heart catheterization and angiocardiography with very rapid intracardial injection of contrast material. These investigations started in September 1954, and since then 50 infants have been examined: 8 of the children included in this material were more than 1 year of age (the oldest 1 year 11 months old), but have been included among the infants, as according to weight, they belong to the younger age group, the heaviest one weighing 9·7 kg. The age and weight distribution is shown in Table I.

A preliminary diagnosis was made in each case based on a routine clinical examination and case history. The relation between the clinical diagnosis and the final diagnosis is seen in Table II. Septal defects were diagnosed clinically in 29 cases without specifying if localized to the atrial or to the ventricular septum as it is seldom possible to differentiate these in this very young age group. The diagnosis was correct in 26 of the cases but, as shown in Table II, incomplete. In 3 cases the left-to-right shunt was due only to a persistent ductus arteriosus. All cases considered, there have been 41 instances where the combination of clinical symptoms allowed a probable diagnosis to be

TABLE I

AGE AND BODY WEIGHT OF PATIENTS

Body weight (kg.)	Age (in months)				
	3 or less	4–6	7–9	10–12	12–24
<3·0	1				
3·1–5·0	11	9		1	
5·1–7·0		8	2	4	1
7·1–9·7			4	2	7
Total ..	12	17	6	7	8

TABLE II

COMPARISON OF CLINICAL DIAGNOSIS AND FINAL DIAGNOSIS

Clinical diagnosis	No.	Final diagnosis	No.	Confirmed by operation only	Confirmed by autopsy
Septal defects with left-to-right shunts.	29	ASD	3	1	
		VSD	11	3	4
		PDA	2	2	
		ASD+VSD	6		2
		ASD+PDA	1		1
		ASD+VSD+PDA	1		
		VSD (" Eisenmenger ")	1		
		VSD with aorta from rudim. outlet chamber	2		
		VSD+PDA+stenosis of aortic valve+" infantile " type of coarctation of aorta	1		1
		PDA+PS	1		1
PDA	1	PDA		1	
Coarctation of aorta	1	Coarctation of aorta	1	1	
Tetralogy of Fallot	6	Tetralogy of Fallot	4		3
		PS+PFO+PDA	1		1
		Complete transposition of the great vessels	1		
PS+ASD	1	Tetralogy of Fallot	1		1
Complete transposition of the great vessels	1	Complete transposition of the great vessels	1		1
Tricuspid atresia with underdeveloped right ventricle	1	As clinical diagnosis+pulmonary artery from left ventricle	1		
Fibroelastosis	1	Fibroelastosis+ASD	1		
Acyanotic, type uncertain ..	6	Isolated PS	1		
		VSD	2		1
		ASD+VSD	2		1
		Uncertain	1		
Cyanotic, type uncertain ..	3	Tetralogy of Fallot	2		1
		do. +PDA	1		
Total	50		50	8	18

Abbreviations: ASD: Atrial septal defects. PFO: Persistent foramen ovale. VSD: Ventricular septal defect. PDA: Persistent ductus arteriosus. PS: Pulmonary stenosis.

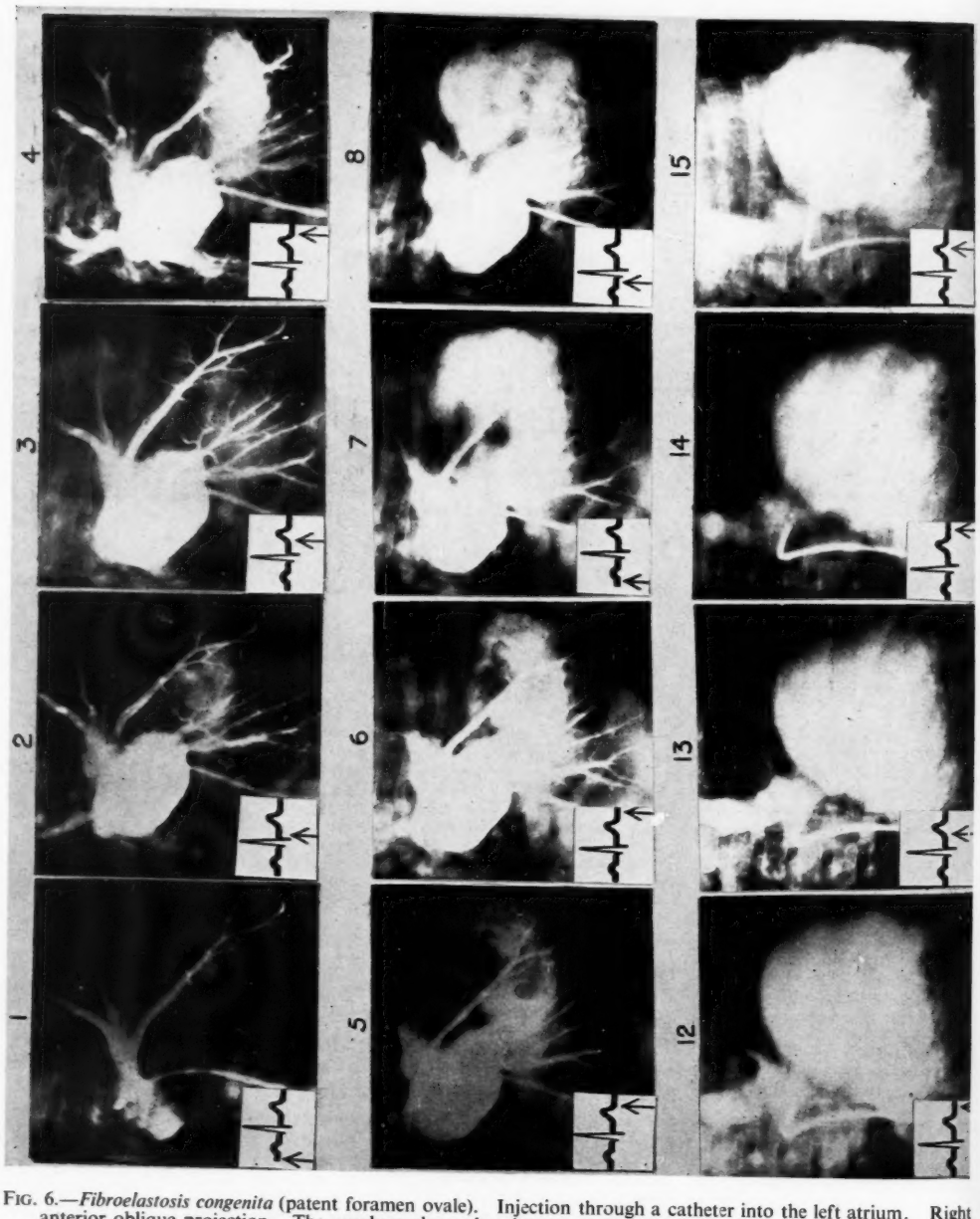

FIG. 6.—*Fibroelastosis congenita* (patent foramen ovale). Injection through a catheter into the left atrium. Right anterior oblique projection. The numbers above the pictures represent the real order of exposures. Rate of exposures 6 pictures per second. The series shows different successive stages of filling and emptying of the left atrium and ventricle. The slow filling and the exceedingly ineffective emptying of the left ventricle are strikingly illustrated.

made. It is possible, therefore, in most cases to make a fairly correct diagnosis. Such a diagnosis is, however, usually not complete enough for surgical consideration, especially for the cases with left-to-right shunts. Complementary examinations are, as a rule, necessary to this end.

Risks. Two patients died the first day after the examination. In the first the examination itself may have aggravated an already pronounced insufficiency to such an extent that the infant could not be saved: the patient was exceptional in being under ether narcosis and was troubled by it, being coughing and restless. The other was a one-month-old boy who died suddenly the day after an intravenous angiocardiography which, in itself, had not affected him at all. According to the angiocardiograms, he probably suffered from a tricuspid stenosis but, unfortunately, the diagnosis was not verified as autopsy was not permitted. It is doubtful whether the angiocardiography could have caused the death. In this connection it should be mentioned that one patient died the day before the planned examination, and two on the morning of the day of the examination.

In one case the injection was unintentionally made into the coronary sinus, in one case into a pulmonary vein, and in one case through the heart muscle into the pericardium. Only the last patient was severely upset (shocked, and with ventricular tachycardia for 30 minutes).

Discussion

There are only a few publications available on the value of *heart catheterization in infants*. Ziegler (1954) has published the results of examinations of 188 children less than one year old and says that the method is simple and often gives quite satisfactory information. The method is, however, not discussed in detail. According to our findings it is hardly possible to transfer all the experiences of heart catheterization in adults to infants.

At heart catheterization three kinds of information are obtained, viz. (1) pressures from the different heart chambers and the great vessels; (2) oxygen saturation of the blood; and (3) abnormal communications that can be directly shown by the passage of the catheter. Concerning the *pressure measurements* in congenital heart diseases they are mainly of importance in the diagnosis of stenoses, but the presence of an increased pressure in the heart cavities in the absence of a stenosis is also of great interest. In 18 of 23 infants with ventricular septal defects with left-to-right shunts, there has been a considerably increased pressure in the right side of the heart (above 50 mm. Hg).

In our observations the pressure conditions in infants are rather unstable during catheterization: they often show considerable respiratory changes. The examinations are made under full or partial anæsthesia. There are thus no normal physiological conditions present. Future examinations may clarify the importance of these circumstances.

From determinations of the *oxygen saturation* of the blood at catheterization of normal subjects it has been found that the difference in oxygen saturation between the pulmonary artery and the right ventricle must be, at least, one volume per cent to permit the diagnosis of a left-to-right shunt. The same holds true about the difference between the right ventricle and the right atrium. Between the right atrium and the venæ cavæ the difference must be at least two volumes per cent. These values are obtained in older children and adults. No normal values are yet known for infants. According to our experience, these differences must be considerably higher in order to make a safe diagnosis of a left-to-right shunt, especially through an atrial septal defect.

Concerning the direct *passage of a catheter through an abnormal communication* between the two circulations, this has been a useful diagnostical method. In 15 of the 50 children examined the left atrium was catheterized, and only in 11 of these were there signs of an interatrial shunt. In 5 cases the aorta was catheterized through the ductus arteriosus.

We agree with Ziegler that heart catheterization in infancy is technically feasible and it is possible to get very valuable information concerning the anatomical diagnosis and the load on the circulation. This is, of course, of utmost value in deciding prognosis and therapy.

Angiocardiography. If detailed information of the anatomical changes in the malformed heart is desired, the examination should be completed with angiocardiography.

Angiocardiography has been used to a great extent in the diagnosis of congenital heart diseases in infants (Castellanos *et al.*, 1937; Lind and Wegelius, 1952). If the problem to be solved is physiological it presupposes that the contrast medium is injected intravenously because this way of introducing the contrast medium into the circulation causes least hæmodynamic disturbances. In a number of cases, however, this method does not give the detailed anatomical information the surgeon needs.

There are several advantages in injecting the contrast medium into the heart. In this way it is possible to get a higher concentration of the contrast material in the part of the heart that is of special interest to be visualized in each individual case. These requirements are best met with if the tip of the catheter lies in the chamber or vessel to be examined.

If the injection is made in the pulmonary artery the contrast reaches the pulmonary veins, the left atrium, and the left ventricle in high concentration. Anomalous pulmonary veins can in this way be visualized directly. A left-to-right shunt through an atrial or ventricular septal defect will be shown in the left anterior oblique projection, as the blood loaded with contrast medium is shunted from the left side of the heart into the right atrium or ventricle, empty of contrast material.

A satisfactory concentration of contrast medium in the aorta is also obtained by this method and this permits a study of the anatomy in cases of coarctation of the aorta.

Using intracardiac injection it seems possible sometimes to increase the pressure in the injected cavity and in this way artificially to reverse the shunt in cases of interventricular left-to-right shunts. By intravenous angiocardiography it is impossible to get exact information of the size and localization of the defect. By intracardiac injection of the contrast medium this may be possible in cases where a right-to-left shunt can be produced in ventricular diastole due to the rapid injection, but is not possible when the shunt is from the right atrium to the left, because in cases of atrial septal defects the left-to-right shunt is continuous through the whole heart cycle.

Finally, it must be stressed, as was originally done by Jönsson *et al.* (1949), that by this method it is possible to take full advantage of the results from the catheterization, considering both the pressures obtained in the various chambers, the oxygen content of blood withdrawn from them, and the rœntgenological aspects of the heart catheterization. Based on these results and the clinical examination, the injection of contrast medium can be carried out in a way that gives optimal information for the diagnosis and for an eventual operation.

Summary

A combination of clinical diagnosis, heart catheterization, and rapid biplane angiocardiography with intracardiac injection of contrast medium has been used in the diagnosis of 50 cases of congenital heart diseases in infants. A satisfactory degree of certainty regarding both the pathological-anatomical changes, as well as the pressure and shunt conditions of the circulation has been obtained. After these investigations it has been possible to refer a number of infants for operation with a much more reliable diagnostic basis than previously.

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ANOMALOUS PULMONARY VENOUS DRAINAGE

BY

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The diagnosis of anomalous pulmonary venous drainage has been made with increasing frequency in recent years (Friedlich *et al.*, 1950 ; Swan *et al.*, 1953; Johnson, 1955; Sepulveda *et al.*, 1955), largely due to the use of cardiac catheterization, and has become more important now that the surgical repair of atrial septal defects is possible. The co-existence of these two anomalies is more frequent than has been realized.

Anomalous pulmonary venous drainage was originally described by Winslow (1739) and isolated cases were reported in increasing numbers during the next two centuries. However, these were regarded at the time as little more than interesting anatomical curiosities. Brody (1942) was able to collect 100 reported cases; of these, 36 per cent had complete, and 64 per cent partial anomalous drainage, and among the latter, the right lung was involved in two-thirds of the cases, and an atrial septal defect was present in over half of those about which there was definite information. Instances were described in which the pulmonary veins were connected, in different cases, to all the great veins within the chest and to the portal vein and ductus venosus, but connection was most common with the superior vena cava or the right atrium. Healey (1952) reviewed reports of 155 cases, of which 40 per cent were of total anomalous drainage and, describing 5 cases from a total of 800 anatomical dissections made by himself and others, suggested that anomalous pulmonary veins are not rare in comparison with other congenital cardiovascular abnormalities.

Anomalous veins from the right lung drain most commonly into the superior vena cava or right atrium and are frequently associated with an atrial septal defect. The latter is usually of limited size and is located posteriorly in close proximity to the mouths of the anomalous veins. However, when one or both of the left pulmonary veins drain into the systemic venous system, they usually do so by way of a left superior vena cava or directly into the coronary sinus. Anomalous veins from the right lung often occur without associated anomalous veins from the left lung, but the reverse is unusual and left-sided anomalous pulmonary veins generally occur with complete transposition of all the pulmonary veins and an atrial septal defect.

In our patients right anomalous veins were present in twelve and left in two (in one patient a single left anomalous vein was present); there was no case of the complete anomaly, probably because none of our patients was under 10 years of age; an atrial septal defect was present in nine and possibly in two more; a left superior vena cava in three; pulmonary stenosis in one; mitral stenosis in two, and an abnormality of the Eustachian valve in one (Hickie, 1955).

EMBRYOLOGY

A brief consideration of the development of the pulmonary veins and interatrial septum will show how anomalous pulmonary veins come to be formed.

In the embryo the lungs develop from the lung bud which forms on the ventral aspect of the foregut, the venous drainage of the lung bud being to the cranial part of the splanchnic plexus surrounding the

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foregut (Fig. 1) (Edwards, 1953; Smith, 1951; Brown, 1913). This plexus is in connection with the sinus venosus and with a number of primitive venous channels in the neighbourhood. As development continues, that part of the venous plexus draining the lung bud forms a single common pulmonary vein, and this comes to enter the sino-atrial chamber by fusion with an outgrowth from the sino-atrial chamber which develops at the same time (Flint, 1906; Squier, 1916; Brantigan, 1947; Edwards, 1953; Buell, 1922; Chang, 1931).

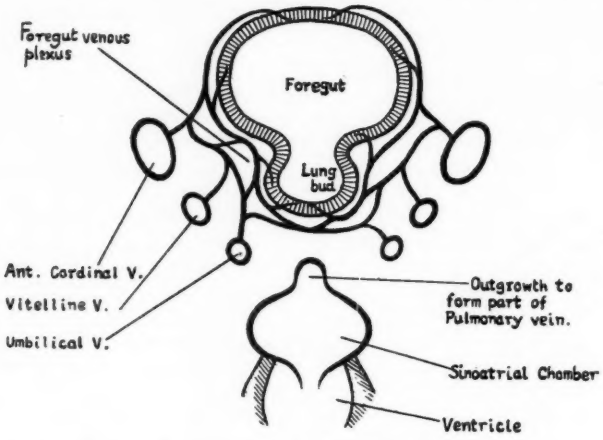


FIG. 1.—Development of lungs and pulmonary veins.

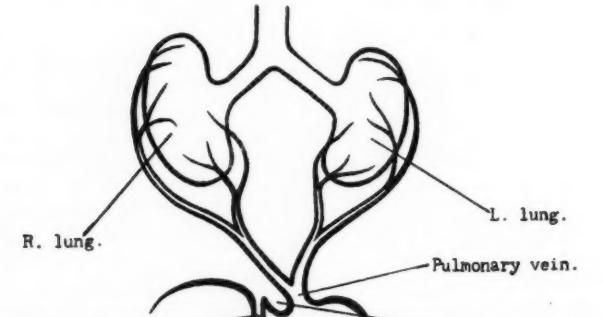


FIG. 2.—Further development of lungs and pulmonary veins.

Later this common pulmonary vein is absorbed into the atrium so that its four branches come to enter the atrium separately; occasionally, however, the common pulmonary vein fails to be absorbed and persists as a supernumary left atrium (Edwards *et al.*, 1951).

The right wall of the newly formed pulmonary vein becomes invaginated into the atrium and forms the pulmonary fold; this separates the opening of the vein from the site of the developing septum primum and leads the pulmonary vein into the left side of the atrial wall clear of the septum. As a result of this process the part of the posterior atrial wall between the septum and the entry of the pulmonary vein is derived from the vein itself (Davies *et al.*, 1937) (Fig. 2). During development of the pulmonary veins there may be failure

of the common pulmonary vein to connect with the outgrowth from the atrium (Edwards *et al.*, 1951) or failure of the common pulmonary vein to form; either state of affairs will result in some of the connections of the pulmonary venous plexus with the rest of the foregut plexus persisting as the route of venous drainage from the lungs (Edwards, 1953; Brody, 1942). Thus the venous drainage of the lungs may be to any of the venous channels with which the splanchnic plexus of the foregut is connected in early development, including the sinus venosus which becomes part of the right atrium. Fig. 3 illustrates the numerous veins with which

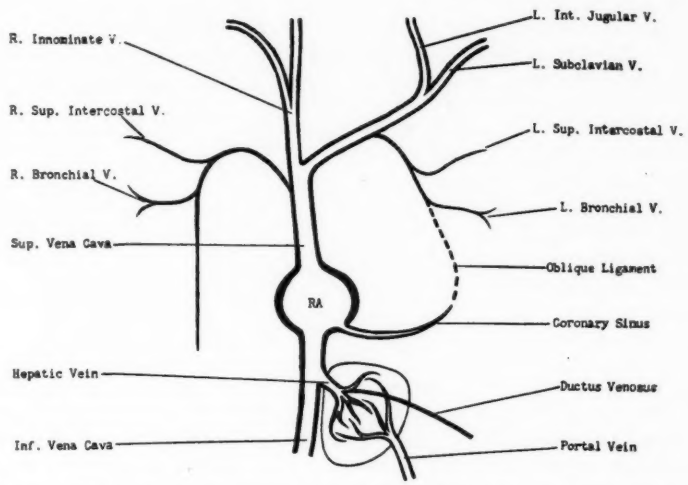


FIG. 3.—This illustrates the numerous veins with which the pulmonary veins may theoretically connect, and with which their connection has been recorded.

the pulmonary veins may theoretically connect, and with which their connection has been recorded (Brantigan, 1947; Healey, 1952) and explains how occasional cases arise where the pulmonary veins connect with such apparently unlikely veins as the portal vein or ductus venosus. It has been suggested that the bronchial veins take over the venous drainage of the lungs when the pulmonary veins fail to form (Conn *et al.*, 1942), but the fact that the bronchial veins normally drain to the azygos and left superior intercostal veins render it unlikely that many of the anomalous pulmonary veins encountered could be enlarged bronchial veins (Edwards *et al.*, 1951; Butler, 1952).

A further explanation of some cases of anomalous connection of the pulmonary veins with the right atrium is that there may be an abnormality in the mode of formation and site of the posterior part of the interatrial septum, so that the pulmonary veins come to enter the atrium partly or wholly on the wrong side of the septum. Failure to form the pulmonary fold is likely to result in the pulmonary veins entering the atrium either to the right of, or occasionally astride, the septum primum; the latter results in a high posterior atrial septal defect with some pulmonary veins entering on one side of the septum, and some on the other (Atkinson *et al.*, 1940).

PHYSIOLOGY

The fundamental disturbance in anomalous pulmonary veins is similar to that found in an atrial septal defect, namely recirculation of oxygenated blood through the lungs. This increased pulmonary flow causes enlargement of the right atrium, right ventricle, and pulmonary artery and may in time cause raised pulmonary arterial and right ventricular pressures. Symptoms probably do not arise unless the anomalous drainage involves at least the whole of one lung (50 per cent or more of the pulmonary flow) or is associated with an atrial septal defect or is part of a more complicated anomaly (Brody, 1942). Single anomalous veins are usually asymptomatic (Mankin *et al.*, 1953; Dotter *et al.*, 1949).

Clinical Features

Clinically it is impossible to differentiate anomalous pulmonary veins and atrial septal defect (Knutson *et al.*, 1950; Mankin *et al.*, 1953; and Johnson, 1955), and as already stressed the two conditions are frequently associated. Complete anomalous pulmonary venous drainage is said to be rare but it was present in 36 per cent of Brody's (1942) series. It is inevitably associated with a patent foramen ovale, an atrial septal defect, a patent ductus arteriosus or a more complicated anomaly. Most cases die in infancy or under six months of age but Snellen *et al.* (1952); Whitaker *et al.* (1954); Bruce *et al.* (1954); and Sepulveda *et al.* (1955) report patients reaching adult life: three of the latter's six patients had the complete defect, the oldest being aged 42 years. Exertional dyspnœa is usually the predominant symptom. There is no diagnostic murmur but occasionally a venous hum may be found over the left upper chest (Keith *et al.*, 1954).

Our experience is limited to 13 patients with incomplete pulmonary venous drainage. The diagnosis was confirmed at operation (Table I) or autopsy in nine. The sex incidence was equal. The symptoms included progressive dyspnœa (13), recurrent bronchitis (7), hæmoptysis (3), præcordial pain (3), exertional giddiness (3), and palpitation (1). The majority of the patients were asymptomatic for many years. Cardiac failure occurred most often in middle age and was usually rapid in onset. The clinical severity of disability in our patients could not be correlated with either the size of the shunt or with the pulmonary arterial pressure and probably depends largely on the state of the myocardium.

Central cyanosis was a feature in 50 per cent of cases. Otherwise the signs were those of increased pulmonary blood flow, namely a palpable pulmonary arterial and right ventricular impulse or præcordial prominence, a pulmonary systolic murmur (10), a pulmonary diastolic murmur (4), a pulmonary systolic click (4), and an accentuated split pulmonary second sound (9). Mitral murmurs (systolic and/or diastolic) were present in five patients but in only one of these was mitral stenosis present at operation or autopsy. In two patients there were no murmurs and in three the murmurs were most unimpressive.

The jugular venous pressure was raised in nine patients but was associated with a palpable liver and slight ankle œdema in only three and in none was gross right heart failure present. In Case 2 the jugular venous pressure was raised on the right side of the neck and appeared normal on the left and at thoracotomy an aneurysm of the superior vena cava was found.

Electrocardiography

The electrocardiographic findings in the present series are similar to those in previous reports of atrial septal defect (Bedford *et al.*, 1941; Routier *et al.*, 1940; Barber *et al.*, 1950) and anomalous pulmonary venous drainage (Whitaker, 1954; Geraci, 1953; and Grishman *et al.*, 1945), and it is impossible to distinguish between the two different types of lesion in this way: in view of their similar effects on the circulation this is not surprising, especially as both may be present.

Eleven of our patients were in normal rhythm, one had auricular flutter, and one auricular fibrillation. It is well known that atrial septal defect is the only congenital heart lesion commonly associated with fibrillation, possibly because there may be mitral stenosis also, and in Bedford, Papp, and Parkinson's series (1941) of 53 cases of atrial septal defect, five of the six with auricular fibrillation had mitral stenosis. Their sixth case was fifty-eight years of age, and they stated that they knew of no reported case of auricular fibrillation in isolated atrial septal defect under fifty years of age. Our Case 9, however, had auricular fibrillation and though there was no operative proof, the low pulmonary capillary pressure and slight rise on exercise render it unlikely that she suffered from mitral stenosis.

P waves were normal in seven of the ten cases in normal rhythm, while in three others they were bifid or abnormally peaked in one or more leads. Bifid P waves in this type of lesion do not necessarily indicate mitral stenosis, and peaked or bifid P waves may be found in the same subject in different leads (Bedford *et al.*, 1941; Brown, 1950).

The P–R interval was increased to more than 0·2 sec. in only one case.

In no case was the QRS complex completely normal. Complete right bundle-branch block occurred only once, incomplete bundle-branch block four times, and what may be described as right ventricular hypertrophy eight times. The latter term is taken to indicate an RSR pattern in V1 and V4R with deep S waves in V3–V6 but where the duration of the QRS does not exceed 0·1 sec. Grishman *et al.* (1949) describe three cases of anomalous drainage of the right lower lobe with associated atrial septal defect, and all showed incomplete right bundle-branch block. Six cases of total anomalous pulmonary venous drainage through a persistent left superior vena cava, with associated atrial septal defect, are reported by Whitaker (1954), and while three of the four children under the age of ten showed the pattern of right ventricular hypertrophy, the two adults showed incomplete right bundle-branch block. Brown (1950), referring to isolated atrial septal defect, states that incomplete is commoner then complete right bundle-branch block, and the view that the block is not a congenital abnormality but is induced by progressive right ventricular enlargement is supported by other authors (Bedford *et al.*, 1941; Routier *et al.*, 1940; Wood, 1950). Taussig (1947) and Sepulveda *et al.* (1955) state that the electrocardiogram may be normal in partial anomalous venous drainage and it seems that the abnormalities are related to the size and duration of the left-to-right shunt. When there is the double pathology there will be a greater left-to-right shunt of blood and right ventricular enlargement, and, therefore, the electrical pattern of right ventricular hypertorphy or bundle-branch block.

X-ray Findings

Radiological findings vary according to the site and origin of the anomalous veins, the vessels into which they drain, and the secondary effects that this re-circulation of blood in the pulmonary circuit has upon the size and shape of the heart. Whether or not there is an associated atrial septal defect there is a continuous left-to-right shunt of blood, the effect of this being to cause right ventricular hypertrophy, dilatation of the pulmonary artery and its branches, and congested lung fields; the aorta is usually small. The cardiac outline is of little or no value, therefore, in differentiating this condition from other lesions that cause a left-to-right shunt.

Turning to the shadows formed by the anomalous veins themselves, two characteristic pictures are found.

(1) When the veins from the left and possibly the right lungs, enter a persistent left superior vena cava draining into the left innominate vein, the abnormal vessel may be seen to the left of the upper mediastinum as a homogeneous bulge, which may be seen on fluoroscopy to pulsate. As a consequence of the increased blood flow into the normal superior vena cava, this in turn dilates, may also pulsate, and the abnormal vascular shadows in the superior mediastinum together with the heart form the characteristic " figure of eight " described by Snellen and Albers (1952) and Gardner and Oram (1953). Our Case 2 showed a dilated and pulsating normal right superior vena cava due to anomalous drainage from the right upper lobe. This was the only instance in our 13 cases of any such radiological abnormality and it disappeared following operation (Fig. 4).

(2) Where there is anomalous drainage into the superior or inferior vena cava the aberrant vessel itself may be seen in the conventional chest film. Many authors (Bruwer, 1953; Snellen *et al.*, 1952; and Sepulveda *et al.*, 1955) describe a comma-shaped shadow parallel to and either inside or outside the border of the heart, which disappears from view at the right cardio-phrenic angle where it joins the inferior vena cava. Grishman *et al.* (1949) point out that these shadows have the homogeneous appearance of a vascular structure, and there is no demonstrable disturbance in the lung fields such as collapse, infiltration, etc. Tomography may sometimes yield further information and in addition to showing the aberrant vessels more clearly it may demonstrate other abnormalities which may co-exist such as bronchial hypogenesis.

Angiocardiography was not employed in any of our cases, although Snellen and Albers (1952) obtained useful information by this method concerning the number of anomalous vessels and their connections. Sepulveda *et al* (1955) employed angiocardiography in all their cases and emphasize

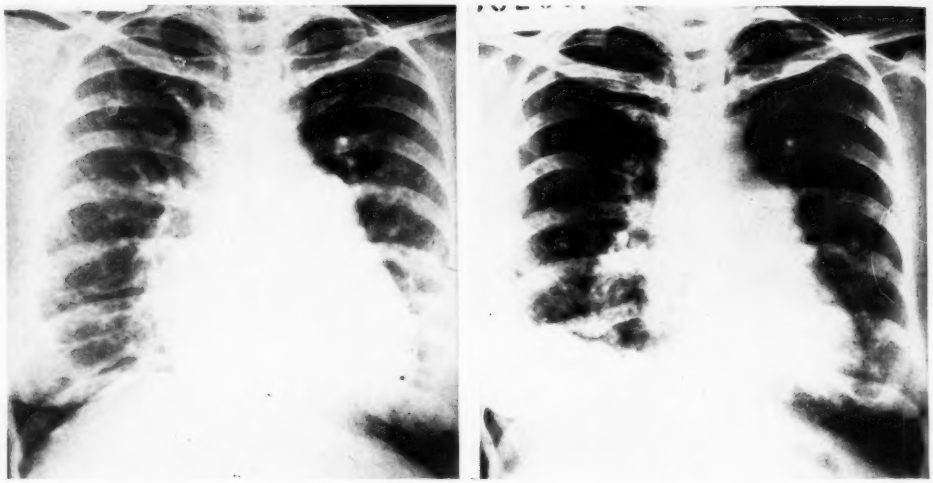
TABLE I

GENERAL FINDINGS IN CASES WITH ANOMALOUS PULMONARY VENOUS DRAINAGE

Case	Sex	Age	History	Signs				E.C.G.	X-ray	Diagnostic features	Subsequent course
				JV.P.	Murmurs	P2	C.C.				
1	F	44	Dyspnœa; pulmonary œdema; R.H.F.	+	P.S.M. & T. P.D.M. M.S.M.	2 ++	+	I R.B.B.B. A. Flut.	R.V.+P.A. +Pul. Cong.	L. to R. shunt in R.A.	A.S.D. created, veins redirected. Good
2	F	46	Dyspnœa; bronchitis; hæmoptysis; pulmonary œdema	+R −L	P.S.M.	1 −	−	R.V.+ Pul. Cong.	R.V.+ P.A.+ Pul. P. S.V.C.++	L. to R. shunt in S.V.C. and R.A.	A.S.D. repair R.S. pul. art. ligated. Improved
3	F	11	Dyspnœa	N	P.S.M. P.S.C.	2 ++	+ C.L.	R.V.+	P.A.+ R.V.+	Catheter entered R.A.P.V. and crossed A.S.D.	Died No autopsy
4	M	56	Dyspnœa; R.H.F.; bronchitis; hæmoptysis	+ "a"	P.S.M. M.S.M.	−	−	I R.B.B.B. Pul. P.	R.V.+ P.A.+	Catheter entered R.A.P.V.	Pneumonectomy Died post-op.
5	M	47	Dyspnœa; bronchitis; præcordial pain	+	M.S.M. M.D.M. P.D.M. P.S.C.	1 ++	+	R.V.+ P.R.O. 24	R.V.+ P.A.+++	Catheter entered R.A.P.V. L to R., R. to L. shunts in R.A.	Cardiotomy Died
6	M	27	Dyspnœa; bronchitis; hæmoptysis	N	P.S.M.	2	+	I R.B.B.B.	PA+ R.V.+	Catheter entered R.A.P.V. and crossed A.S.D.	Repair of A.S.D. Died
7	M	10	Dyspnœa, bronchitis	N	P.S.M. & T. P.D.M.	2 ++	−	R.V.+	R.V.+ P.A.+	Catheter entered L.S.V.C. and A.P.V. L. to R. shunt R.A.	—

8	F	16	Dyspnœa	+ "a"	P.S.M. & T. M.D.M.	2 ++	−	I R.B.B.B. Pul. P.	R.V.+ P.A.+	L. to R. shunt R.A.	Cardiotomy
9	F	42	Dyspnœa; R.H.F.	+	P.S.M. & T. P.D.M. M.D.M.	2 ++	−	R.B.B.B. A.F.	R.V.+ P.A.+	L. to R. shunt R.A.	—
10	M	12	Dyspnœa; cyanosis	N	P.S.M. & T.	1	+	R.V.+	R.V.+ P.A.+ oligæmic lung fields	L. to R. shunt R.A. P.S. Catheter entered R.A.P.V.	Pulmonary valvotomy. Improved
11	M	50	Dyspnœa; paradoxical embolism	+ "a–v"	P.S.M.	2 ++	−	R.V.+	R.V.+ P.A.+	Catheter entered R.A.P.V.	—
12	F	40	Dyspnœa; recurrent pleurisy	+	Nil	2 ++	+	R.V.+	R.V.+ P.A.+	Catheter entered R.A.P.V. L. to R. and R. to L. shunts R.A.	—
13	M	20	Fatal pulmonary œdema	+	Nil	2 ++	+	R.V.+	Pul. oed. Clear Lt. zone	Unusual X-ray	Died

R.H.F. Right heart failure
T. Thrill
P2 Second sound, pulmonary area. 1 single, 2 split, ++ accentuated
R.S. Right superior
P.S.M. Pulmonary systolic murmur
M.S.M. Mitral systolic murmur
P.S.C. Pulmonary systolic click
C.L. Clubbing
P.D.M. Pulmonary diastolic murmur
M.D.M. Mitral diastolic murmur
C.C. Central cyanosis
R.A.P.V. Right anomalous pulmonary vein



A B

FIG. 4.—Aneurysmal superior vena cava before operation (A), and its reduction to normal after operation (B). Case 2.

the importance of the method in the differentiation from uncomplicated atrial septal defect. They also describe a previously unrecognized radiological sign, in the filling defect produced in the atrium, superior vena cava, or left innominate vein at the site of insertion of the anomalous pulmonary vein by the stream of blood from the vein itself deflecting the contrast medium.

All our cases except one (Case 10) showed the radiological picture of increased flow in the pulmonary circuit, and in this instance the anomalous vein was discovered by accident during catheterization. It is important to state that none of our 13 cases was suspected radiologically of having anomalous pulmonary veins although the increased pulmonary flow was clearly visible. Case 13 was unique in that the classical radiological picture of pulmonary œdema was associated with a normal left upper lung zone. The significance of this was not appreciated at the time, but it was later found to be due to anomalous venous drainage of the left upper lobe to a left superior vena cava and right atrium in the presence of mitral stenosis and an intact septum. The anomalous drainage protected this lobe from the general circulatory disturbance (Fig. 5).

CARDIAC CATHETERIZATION

It has been pointed out that there is no means of diagnosing the presence of anomalous pulmonary veins clinically, and the diagnosis during life has usually been made at thoracotomy or by means of special investigations; of these, cardiac catheterization is the most informative.

The presence of anomalous pulmonary veins should be considered in all cases of congenital heart disease, and in particular when a diagnosis of atrial septal defect has been made. The discovery of abnormalities of the systemic veins is suggestive. After the catheter has entered the right atrium it may enter a pulmonary vein (Fig. 6 and 7) and then the difficulty arises of being certain whether or not it has first passed through an atrial septal defect. Generally, if the catheter enters a vein from the right lung it is possible to demonstrate without reasonable doubt that the vein is connected to the right atrium by moving the patient under the X-ray screen; the operator can then observe that the catheter has passed straight down the right border of the heart and into the lung without coiling inside the heart shadow (Johnson, 1955; Snellen *et al.*, 1952). If there is doubt, it is helpful to obtain a sample of blood from the vein itself and another on withdrawal as soon as the tip

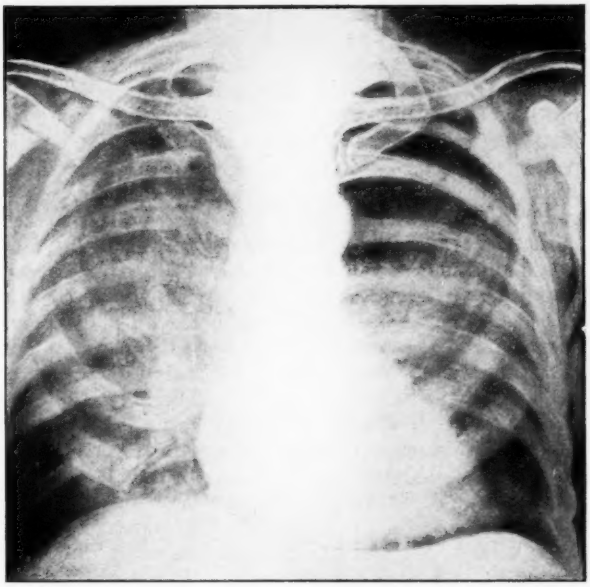


FIG. 5.—Drawing of radiograph of Case 13. Typical picture of pulmonary œdema without involvement of the left upper lobe which had an anomalous venous drainage.

FIG. 6.—Radiograph of Case 3, showing typical appearance of cardiac catheter passing from right atrium into an anomalous right pulmonary vein.

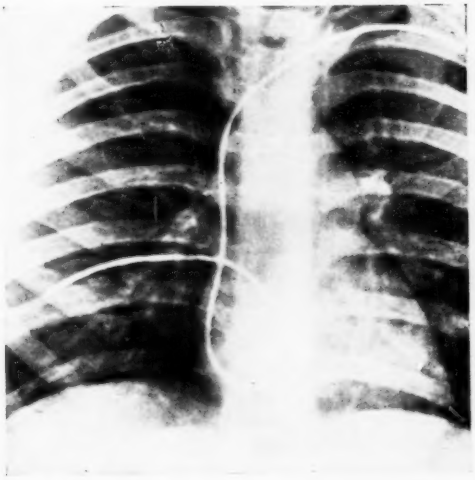


FIG. 7.—Radiograph of Case 10 with cardiac catheter entering an anomalous right pulmonary vein. When this has previously coiled in the right atrium it may be difficult to distinguish from a catheter that has entered a normal pulmonary vein via an atrial septal defect.

of the catheter leaves the vein and re-enters the cardiac shadow. If the second sample is less saturated than the first, it suggests that the vein in question is entering the right atrium. Dye injection studies are also helpful in this situation (Swan *et al.*, 1953; and Broadbent, 1951; see below).

In all cases where it is likely that anomalous pulmonary veins are present it is important to take at least two samples of blood from the right atrium and one each from the superior and inferior vena cava and an innominate vein, because it is not always possible to demonstrate an anomalous pulmonary vein by passing a catheter into it, and its presence can be inferred when blood samples show evidence of a shunt of oxygenated blood into the right atrium or one of the great veins. If the shunt is demonstrated only in the right atrium it could well be due to an atrial septal defect alone, and in these circumstances dye studies may decide the point (see below).

Calculations of flows and shunts can be attempted by the use of established formulæ, but the results may be invalidated due to the presence of an atrial septal defect. It is difficult to separate the effect of the latter, and also the variation in a shunt from moment to moment with variations in heart rate, respiration, and the oxygen content of the inspired air (Swan *et al.*, 1953).

The results of cardiac catheterization are shown in Table II. All the cases showed evidence of a considerable left-to-right shunt, as might be expected, and a right-to-left shunt was probably present in the eight cases known to have an atrial septal defect. It is noteworthy that the systemic arterial saturation was well below normal in these eight, and in one case with no atrial septal defect (Case 1). The saturation of the pulmonary venous blood was also below normal in three of the five cases in which it was estimated. This contrasts with the findings of other authors (Snellen *et al.*, 1952; Johnson, 1955; and Friedlich *et al.*, 1950) who have found the blood in the anomalous veins to be fully saturated. Pulmonary vascular changes were suspected to be responsible for the low saturation in our cases but unfortunately no histological confirmation was obtained. Significant pulmonary hypertension was present in ten cases and pulmonary stenosis in one : the latter is said to be rare in association with anomalous veins but was present in two of the five cases reported by Sepulveda *et al.* (1955).

Oximetry

Dye concentration dilution curves were obtained in six patients using T.1824 injected via the cardiac catheter and an ear oximeter (Swan *et al.*, 1953). By this method it was possible to demonstrate a degree of right-to-left shunt at the atrial level in two patients (Cases 5 and 6) and thereby infer that an atrial septal defect was present although the catheter was not passed through it. In both these cases the associated pulmonary venous anomaly was proven by the entry of the catheter into one of the anomalous veins. Later this was confirmed post mortem. In all six a prolonged descending limb of the dye concentration dilution curve indicated a left-to-right shunt. As this effect could be produced both from an atrial defect or from anomalous venous drainage alone or in conjunction with one another it is often difficult to make a firm diagnosis of the presence or absence of such a combined lesion using this technique.

Treatment

The indications for surgical treatment in this condition are the same as those applying to atrial septal defect. A decision that the physician will have to make is whether to confine operative treatment to those with severe disability and thus present the surgeon with poor operative risks, or whether to advise those with high pulmonary blood flow or pulmonary hypertension to submit to an operation that is as yet far from standardized while they themselves are little disabled. Surgical treatment has undergone and is still undergoing changes, and with the increasing safety of operation in the future one may tend to advise it at an earlier date.

The importance of anomalous pulmonary veins was realized many years ago during routine lobectomy and pneumonectomy, and failure to recognize them at operation may be serious or fatal (Healey, 1952; Hwang, 1950). Brantigan (1947) suggested that if there was anomalous drainage of

TABLE II

CARDIAC CATHETERIZATION DATA

Case No.	Anatomical findings	Pressures (mm. Hg)				Percentage oxygen saturation					
		R.A.	R.V.	P.A.	P.C.	S.V.C.	I.V.C.	R.A.	R.V.	P.A.	B.A.
1	3 A.P.V., No A.S.D.	M.10	85/6	69/36	—	65	—	80	79	83	87
2	Rt. A.P.V. into S.V.C., A.S.D. aneurysmal S.V.C.	M.3	60/0	56/18	20/8	81	innom. v. 68	84	87	86	91
3	Rt. upper A.P.V., A.S.D.	—	90/16	M.96	—	55	—	59	68	65	—
4	Complete Rt. A.P.V., A.S.D., Lt. S.V.C.	4/-1	50/0	45/13	30/15	55	75	76	80	76	89
5	Complete Rt. A.P.V., A.S.D.	12/8	95/8	105/45	—	52	59	73	70	71	80
6	Complete Rt. A.P.V., A.S.D.	15/8	36/5	36/16	M.7	—	—	79	75	75	90
7	Lt. S.V.C., Lt. A.P.V., ? A.S.D.	11/8	71/5	71/44	12/11	Lt. S.V.C.92	64	71	82	86	—
8	Complete Rt. A.P.V., A.S.D.	1/-2	40/0	23/11	—	63	85	86	85	85	86
9	Rt. lower A.P.V., ? A.S.D.	M.7	35/0	33/15	M.10	56	63	82	81	79	91
10	Complete Rt. A.P.V., ? A.S.D., P.S.	6/0	126/0	15/5	M.6	63	70	80	68	—	—
11	Rt. A.P.V., ? A.S.D.	—	—	95	—	61	59	72	74	74	85
12	Rt. A.P.V., A.S.D.	16/11	108/15	105/50	M.25	63	72	82	67	73	80
13	Lt. A.P.V., M.S.	—	—	—	—	—	—	—	—	—	—

Samples were taken from the anomalous pulmonary veins in five cases and these were fully saturated in two but only 87% saturated in three.

pulmonary blood into the major systemic veins the patient would be benefited by removal of that portion of the lung anomalously drained. In our series pneumonectomy was performed only in Case 4, where the whole of the right lung drained into the right atrium. Unfortunately this patient died of collapse of his remaining lung.

Swan and Mulligan (1948) have demonstrated that a single pulmonary vein can be ligated in the dog and the animal will survive, but that if all the veins from one lung are ligated the result is usually fatal. There is no report of such a procedure in man. In Case 2, ligation of the pulmonary artery to the affected lobe was performed together with closure of an atrial septal defect, and the large pulsating superior vena caval shadow, into which the anomalous pulmonary vein drained, has since disappeared.

Gerbode (1950) showed that large veins could be anastomosed to the left atrium without causing serious disturbance in cardiac function during the procedure, and he pointed out the usefulness of a persistent left superior vena cava for this purpose.

Attempts to correct complete anomalous pulmonary venous drainage have been made in a few cases (Muller, 1951; Snellen and Albers, 1952; Gardner and Oram, 1953; Friedlich *et al.*, 1950; Neptune *et al.*, 1953; and Keith, 1954), but the repair of partial anomalous pulmonary vein drainage, with or without a co-existent atrial septal defect, has been more common (Neptune, 1953; Kirklin, 1953; Johnson, 1955). Bailey (1955) recommends a variety of surgical procedures designed to deal with single and double right anomalous pulmonary vein with and without atrial septal defect, with anomalous left pulmonary veins, and with complete anomalous pulmonary venous drainage. For details the original should be consulted.

Summary

Thirteen patients with incomplete anomalous pulmonary venous drainage are described. The diagnosis was confirmed at operation or autopsy in nine. Right anomalous pulmonary veins were present in twelve and left anomalous veins in two, an atrial septal defect in nine and possibly two more, a left superior vena cava in three, pulmonary stenosis in one, mitral stenosis in two, and an abnormality of the Eustachian valve in one. The right anomalous veins drained into the superior vena cava or right atrium, and the left veins into a left superior vena cava. The association of right anomalous pulmonary veins and atrial septal defect (usually a posterior one) is common.

The embryology of the pulmonary veins and their association with the atrial septum and the great veins within the chest is discussed.

This anomaly may be complete or incomplete. The complete anomaly was not present in this series but is described. In our patients exertional dyspnœa, recurrent chest injections, hæmoptysis, præcordial pain, and exertional giddiness were the common symptoms. The majority were asymptomatic for many years and cardiac failure when it occurred was rapidly progressive.

The fundamental physiological disturbance is increased pulmonary blood flow which may lead to pulmonary hypertension (10 out of 13). The signs are therefore similar to those found in atrial septal defect. In one patient a unilateral abnormality of the jugular venous pulse was found. In the electrocardiogram 11 patients had normal rhythm, one auricular flutter, one auricular fibrillation, eight right ventricular hypertrophy, four incomplete, and one complete, right bundle-branch block.

Radiologically all patients had cardiac enlargement mainly due to right ventricular hypertrophy and increased prominence of the pulmonary artery and its branches. In one there was an aneurysmal dilatation of the superior vena cava. Figure-of-eight and comma-shaped shadows are mentioned although not present in this series. An unusual radiological picture in a patient with pulmonary œdema is described.

Angiocardiography is informative. Cardiac catheterization was performed in twelve patients and yielded the most useful information. The catheter may enter an anomalous vein or may show evidence of a left-to-right shunt.

Oximetric studies following injection of Evans' blue were performed in six patients, and gave

useful information in all and diagnostic help in two in whom a degree of right-to-left shunt was present.

The surgical treatment of the condition is reviewed.

The diagnosis of this anomaly requires a variety of procedures because of the difficulties of distinguishing atrial septal defect and anomalous pulmonary veins alone or in combination. It is becoming increasingly important because of its frequency as a chance finding during cardiac catheterization and the need for its recognition before operations for atrial septal defects.

We wish to express our thanks to Dr. R. W. D. Turner for details of Case 12, to Dr. R. Jeremy of Sydney for permission to include Case 13, to Miss J. Dewe for Fig. 8 and to the Department of Medical Photography for the other illustrations. In particular we are grateful to Dr. Raymond Daley for his advice and encouragement, and to Dr. G. de J. Lee for the oximetric investigations.

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SELECTION FOR ANTICOAGULANT THERAPY IN CARDIAC INFARCTION USING THE HEPARIN RETARDED COAGULATION TIME

BY

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In an earlier publication (Peel, 1953) it was suggested that a modified form of Rosenthal's (1949) " Heparin-retarded coagulation time " (HRCT) could be used as a basis for determining the need for anticoagulant treatment in cardiac infarction. Preliminary findings showed a higher mortality and more frequent thrombo-embolic complications in patients with a short HRCT, although anticoagulants were given to them and withheld from those with a normal or prolonged HRCT. The present paper gives the results of four years' experience in the use of this method of selection.

Material

Although testing and selection have been carried out on patients seen at any time during the acute stage of coronary thrombosis only patients seen within seven days of the onset are considered in discussing the immediate prognosis and mortality (up to the end of the sixth week). The first week is by far the most dangerous period after a cardiac infarct. In a series of patients seen prior to 1950 (Peel, 1955), there were 45 deaths up to the end of the sixth week; of these, 17 occurred within four days, and 22 within seven days of the onset. Table I shows how the mortality figure in that series is affected by inclusion of patients who were not seen in the initial days of the attack. The highest mortality figure is obtained when patients seen within 48 hours of the onset are considered by themselves. The figure is only slightly reduced by inclusion of patients seen up to the end of the first week; but when those coming under observation for the first time in the second, third or fourth week are included, the apparent mortality is progressively lowered. In order to

TABLE I

Mortality of Cardiac Infarction as Affected by Inclusion in the Series of Patients seen for the First Time in the Later Stages of an Attack. 1930/50 Series; Not HRCT Tested; No Anticoagulants used

First seen	Number traced to end of sixth week	Deaths	Mortality (%)
Within 24 hours ..	57	15	26·3
,, 48 ,, ..	91	25	27·5
,, 4 days ..	132	33	24·8
,, 7 ,, ..	144	36	25·0
,, 14 ,, ..	174	41	23·5
,, 21 ,, ..	187	42	22·4
,, 28 ,, ..	198	43	21·7
,, 42 ,, ..	209	45	21·5

make it strictly comparable with the present series, the 1930/50 series has been re-analysed after excluding all patients who were first seen on the eighth day or later; details are given in Table II.

TABLE II

CARDIAC INFARCTION

Patients seen within seven days of onset. Mortality up to end of sixth week

History	Sex, age, shock failure	1930/50 No anticoagulants (not HRCT tested)			1951/54 Selection for anticoagulants based on HRCT test		
		Traced	Died	Per cent	Traced	Died	Per cent
First attack No previous cardiovascular symptoms	MALES						
	28–49	8	0	Nil	10	0	Nil
	50–64	33	6	18·2	17	2	11·7
	65–85	8	3	37·6	17	2	11·7
	Unknown				2	0	
	Total	49	9	18·3	46	4	8·7
	FEMALES						
	40–64	2	1		6	0	
	65–85	2	1		4	1	
	Total	4	2		10	1	
	SHOCK						
	+	28	10	35·8	18	4	22·2
	−	25	1	4·0	38	1	2·6
	CARDIAC failure	19	8	42·1	21	3	14·4
Previous coronary thrombosis, angina, exertional dyspnœa, hypertension, peripheral or cerebral vascular disease	MALES						
	28–49	10	1	10·0	10	1	10·0
	50–64	36	4	11·1	41	10	24·4
	65–85	15	5	33·3	19	10	52·8
	Unknown				2	0	
	Total	61	10	16·4	72	21	29·2
	FEMALES						
	40–64	9	3		8	1	
	65–85	8	1		13	7	
	Total	17	4	27·8	21	8	38·1
	SHOCK						
	+	44	13	29·6	38	19	50·0
	−	34	1	3·0	55	10	18·2
	CARDIAC FAILURE	21	5	23·8	34	14	41·2
CASES EXCLUDED							
Died during examination		9	9		3	3	
Moribund when seen					7	7	
Unsuitable for HRCT as heparin already given					15	4	
Short HRCT but refused treatment					3	1	
No facilities for test					5	0	
Total		140	34	24·2	182	49	26·9

Patients who were considered moribund when seen have been excluded both from the present series and from the revised 1930/50 figures. There were 9 such cases in 1930/50, and 10 in 1951/54; three of the latter actually died while being clinically examined. These 19 cases consisted of two men aged under 50, six aged 50–64, and seven aged 65 or over; with one women under 50 and three over 65.

In practice it proved impracticable to test 23 patients and to order treatment accordingly. Thus three patients with an accelerated HRCT refused anticoagulant treatment; fifteen were unsuitable for testing as they had already been given heparin by their own doctor, and in the circumstances the treatment was simply continued without the selective test; finally, five patients were seen unexpectedly when tubes for the test were not available and these received no anticoagulants. Details of these excluded cases are given in Table II. There remain 149 patients in whom the test was used as the criterion for giving or withholding anticoagulants.

The technique of the test has already been described (Peel, 1953). Early in 1954 a minor modification was introduced when the apparent commencement of clotting was recorded as well as the end point, the result being expressed as " 15–18 " or " 32–40," etc. In most cases the decision for or against anticoagulant treatment was unaffected by this modification. In 11 instances, however, clotting commenced in less than 20 minutes, but was still incomplete in 20 minutes. These cases would not have received anticoagulants prior to 1954; nevertheless, ten were given anticoagulants and have been included in the " short HRCT " group. The eleventh patient received no anticoagulants and is included in the " normal HRCT " group; he died suddenly and unexpectedly during the third week.

The anticoagulant used during the first two years of this study was ethyl biscoumacetate (tromexan), and during the last two years phenylindanedione (dindevan). In either case heparin has been used at the start of treatment until satisfactory prolongation of the prothrombin time has been obtained, and also later in treatment whenever the prothrombin time has dropped temporarily below the desired level. A prothrombin level of two-and-a-half times the control figure has been the aim; heparin has been given when the level has been less than twice the control value. No hæmorrhagic complications have been encountered. We have noted no difference in the ultimate results with dindevan as compared with tromexan, but we are convinced that dindevan is more easily controlled, produces a more constant prolongation of prothrombin time, and requires fewer changes in dosage. Anticoagulants were given for three weeks initially; subsequent treatment was based on the HRCT.

Results and Discussion

The importance of age and sex in any consideration of the mortality of cardiac infarction has already been stressed (Peel, 1955). A further factor that has turned out to be of supreme importance in relation to the present investigation is the patient's previous history. The difference between patients with and those without a history of previous cardiovascular disease is so great that it is necessary to discuss them separately; and they have been kept separate in all relevant tables. Prodromal symptoms preceding an attack for a few days or weeks have not been regarded as constituting " previous cardiovascular disease "; this has been accepted as present when there has been a history of angina of effort or exertional dyspnœa at a constant level over a period of months or years, a previous coronary thrombosis, a cerebral vascular accident, peripheral vascular disease, or pre-existing hypertension.

First Attacks without Preceding Cardiovascular Disease. It is clear that in this group the method of selection has met with considerable success. The mortality was halved as compared with 1930/50 (Table II). The improvement is seen in both sexes and at all ages; it is particularly striking in the older age group which normally carries a much higher risk. Table III shows that the test is capable of selecting a group of patients who do not require anticoagulants; there was not a single death among the 28 patients whose HRCT remained normal; of the five deaths, four occurred in

TABLE III

CARDIAC INFARCTION

1951/54 series analysed

History	Sex, age, shock failure	HRCT under 20 (anticoagulants given)			HRCT over 20 (anticoagulants withheld)			HRCT normal at first, later accelerated; A/C started then	
		No.	Died	Per cent	No.	Died	Per cent	No.	Died
First attack No previous cardiovascular symptoms	MALES								
	28–49	3	0		6	0		1	0
	50–64	8	2		9	0		0	0
	65–85	8	1		8	0		1	1
	Unknown	0	0		1	0		1	0
	Total	19	3	15·8	24	0	Nil	3	1
	FEMALES								
	40–64	2	0		3	0		1	0
	65–85	3	1		1	0		0	0
	Total	5	1	20·0	4	.0	Nil	1	0
	SHOCK								
	+	15	4	26·6	2	0		1	0
	−	9	0		26	0		3	1
	CARDIAC FAILURE	11	3		10	0		0	0
Previous coronary thrombosis, angina, exertional dyspnœa hypertension, peripheral or cerebral vascular disease	MALES								
	28–49	9	1	11·1	1	0		0	0
	50–64	20	4	20·0	14	3	21·4	7	3
	65–85	9	5	55·6	8	4	50·0	2	1
	Unknown	2	0		0	0		0	0
	Total	40	10	25·0	23	7	30·4	9	4
	FEMALES								
	40–64	8	1		0	0		0	0
	65–85	10	6		2	0		1	1
	Total	18	7	38·8	2	0		1	1
	SHOCK								
	+	23	10	43·5	10	5	50·0	5	4
	−	35	7	20·0	15	2	13·3	5	1
	CARDIAC FAILURE	20	8	40·0	9	2	22·2	5	4

patients whose HRCT was short and who received anticoagulants from the start; three were sudden and unexpected while the fourth was due to rupture of the infarct. The fifth death was in a man of 66 whose HRCT was prolonged (60 minutes) on the first day; it became accelerated (17 minutes) on the fourth day and anticoagulants were then started; paroxysmal auricular fibrillation appeared on the seventh day, intermittent ventricular tachycardia on the twelfth day, while on the eighteenth day he had a lung infarct; he died suddenly on the twentieth day.

On the basis of the 1930/50 figures, the deaths " expected " in 1951/54 total 15, made up as follows: men 50–64, four; 65–85, six; women 40–64, three, 65–85, two. As the 28 patients with a normal HRCT were treated exactly like the 1930/50 cases and yielded no deaths, the " expected "

deaths must be assigned to the group of 28 patients whose HRCT was accelerated from the start or became accelerated later, an " expected " mortality of 53·6 per cent. The experienced mortality was 17·8 per cent in this group, and the difference is a measure of the benefit of anticoagulant treatment in those patients who genuinely require it. Although intravenous noradrenaline drip transfusions were used in some of the patients who had a history of previous cardiovascular disease, they were not needed or used in any of these patients without a preceding cardiovascular history, the administration or anticoagulants being the only respect in which treatment differed from that given to the 1930/50 cases and the 1951/54 " normal HRCT " cases.

Contrary to our earlier experience, there seems to be a definite relationship between the HRCT and the presence or absence of shock in these patients with first attacks. Shock was present in 15 of 24 patients in the " short HRCT " group, but in only 2 of 28 with a normal HRCT. On the other hand, failure was only a little less frequent in those with a normal HRCT (10 out of 28) than in those with acceleration (11 out of 24).

Follow-up figures to the end of the first year are still incomplete, but information available to date shows 7 recurrences and 2 instances of embolism among 24 " short HRCT, anticoagulant-treated " cases (37·5%) as compared with 3 recurrences and no emboli among 27 " normal HRCT, no anticoagulant " cases (11%). On the other hand, deaths were fewer in the anticoagulant-treated group (4=17% as compared with 7=26%).

History of Preceding Cardiovascular Disease Present. In the presence of a history of preceding cardiovascular disease, the results both of HRCT testing and of anticoagulant treatment can only be described as depressing. In the 1930/50 series there was little difference between those with and those without previous cardiovascular disease (Table II); but a number of such patients were seen rather late in their illness, and the figures quoted in our earlier publication (which include patients seen after the eighth day) show a slightly higher mortality in those with preceding cardiovascular symptoms. On the other hand, in 1951/54 the mortality was very much higher (31% as compared with 18%) and it was three times the mortality of those with no previous cardiovascular disease. The increased mortality was distributed more or less uniformly among all groups, irrespective of the HRCT and of the giving or withholding of anticoagulants. The death rate in the anticoagulant-treated cases was 32 per cent and in the " normal HRCT " group who received no anticoagulants it was 28 per cent. The high mortality cannot, therefore, be attributed to the withholding of anticoagulants, but would seem to be related to the extent of pre-existing cardiac damage. Furthermore, the figures suggest that, while anticoagulants may conceivably be of prophylactic value in warding off an attack in such patients, they are of no therapeutic value once the attack has occurred.

The relationship between the HRCT and shock no longer holds good in patients with previously damaged hearts. Shock was present in 23 out of 55 with a short HRCT and in 10 out of 25 with a normal HRCT. Failure was present in 18 of 55 with a short HRCT and in 9 of 25 with a normal HRCT. On the other hand the test still gave a reasonable index of the danger of extension of the infarct or of embolism. There were five deaths from extension and two from embolism among the 58 patients with a short HRCT (despite anticoagulant treatment); one death from extension and one from embolism among 10 patients whose HRCT became accelerated later; but only one death from extension and none from embolism among the 25 patients whose HRCT remained normal. The high mortality in this latter group is made up with three deaths from failure (12%) and three sudden deaths (12%).

The later follow-up in these patients presents a much less gloomy picture. The mortality to the end of the first year was almost identical with that in 1930/50, and little different from that of patients with no preceding cardiovascular disease (Table IV). Once again, recurrences and emboli were more frequent in those who had received anticoagulant treatment because of a short HRCT (six instances among 32 patients, 18·7%) than in those whose HRCT was normal and who received no anticoagulant (one instance among 23 patients, 4·4%).

TABLE IV

CARDIAC INFARCTION

Follow-up of Survivors to end of first year

	1930/50	1951/54 Total	1951/54 series analysed	
			Short HRCT* (A/C+)	Normal HRCT (No A/C)
NO PREVIOUS CARDIOVASCULAR DISEASE				
Survivors, 29th day.. ..	129	118	38	77
Twelve months, traced ..	89	51	24	27
Recurrence	7	10	7	3
Embolism	2	2	2	0
Thrombo-embolism (%) ..	10·1	23·6	37·5	11·1
Deaths	12	11	4	7
Mortality (%)	13·5	21·6	16·7	25·9
PREVIOUS CARDIOVASCULAR DISEASE				
Survivors, 29th day.. ..	128	97	75	78
Twelve months, traced ..	87	55	32	23
Recurrence	8	6	5	1
Embolism	5	1	1	0
Thrombo-embolism (%) ..	14·9	12·7	18·7	4·4
Deaths	20	13	8	5
Mortality (per cent) ..	23·0	23·6	25·0	21·7

* Seven patients whose HRCT was originally normal but became accelerated subsequently are included in the "Short HRCT" group in this table; among these there were two recurrences (non-fatal), two deaths, and no instances of embolism.

Note.—In addition to cases seen within seven days of onset, this table includes those first seen between the eighth and twenty-eighth days (151 in 1930/50, 100 in 1951/54).

Prophylactic Use of Anticoagulants in Cardiac Ischæmia. Cases of cardiac ischæmia seen during 1951/54 have been HRCT tested and those with a short HRCT have been given a prophylactic course of anticoagulant treatment. The results are compared in Table V with those found in 1930/50 when no anticoagulants were used. The incidence of infarct in 1930/50 was 11 per cent within six weeks of onset. In 1951/54 the incidence was 7 per cent in patients with a normal HRCT and 8 per cent in those with a short HRCT who received prophylactic treatment.

TABLE V

CARDIAC ISCHÆMIA; INCIDENCE OF INFARCTION WITHIN SIX WEEKS OF ONSET

	Total seen	Traced 6 weeks	Developed infarct	Incidence (%)
1930/50	167	150	17	11·3
1951/54 Short HRCT (A/C treated)	48	39	3	7·7
1951/54 Normal HRCT (untreated)	78	59	4	6·9

Summary

Rosenthal's " heparin-retarded coagulation time " test has been used in 149 cases of cardiac infarction, those with acceleration of clotting being treated with anticoagulants, while those with a normal or prolonged clotting time received no anticoagulants.

In patients who had no history of previous cardiovascular disease this procedure halved the mortality. Anticoagulants were unnecessary in those whose HRCT remained normal; there were 28 such patients with no deaths. In those with accelerated HRCT, anticoagulants reduced an " expected " mortality of 54 per cent to 18 per cent. Recurrence or embolism within one year was three times more frequent in those with a short HRCT than in those with a normal HRCT.

In patients with a history of previous cardiovascular disease the mortality remained high irrespective of the HRCT, and anticoagulants seemed incapable of reducing it. Nevertheless, death from extension of the infarct or from embolism was more frequent when the HRCT was accelerated, in spite of anticoagulant treatment.

The test was also used in 126 cases of cardiac ischæmia to determine the need for prophylactic anticoagulant treatment; the incidence of infarction within six weeks of the onset of ischæmia was reduced from 11 per cent in an earlier series, to 7 per cent in this series.

I would again acknowledge with thanks the invaluable help of numerous general practitioners who have given information regarding the subsequent course of their patients; of my secretaries Miss A. E. Watson and Mrs. E. Yarr; of the staff of the Pathology Department and of the residents at the Victoria Infirmary.

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FURTHER STUDIES ON THE CEREBRAL BLOOD FLOW ESTIMATED WITH THORIUM-B-LABELLED ERYTHROCYTES

BY

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Since our first preliminary report (Nylin and Blömer, 1955) we have continued our studies on the cerebral blood flow with radioactive-labelled erythrocytes. The experimental conditions have been the same as before, with the exception that one of us (H. B.) has used a special technique for blood sampling. Blood is drawn simultaneously from both jugular bulbs. In a rotating disc two rows of test tubes are inserted and the disc placed within an exicator, which is evacuated to a fixed pressure. With this arrangement it is possible to fill two test tubes simultaneously at constant time intervals. A somewhat similar apparatus has been constructed by one of us (G. N.), but as it has not been used in observations described in this report, it will be described and published later.

The same method as in our first report has been applied for labelling the erythrocytes with thorium B as well as for measuring the activity. Mathematical calculations of the cerebral blood flow have been carried out in the same way as in our first report, but some other relationships have also been computed. Thus, the cardiac output from the dilution curves from the jugular bulbs after intravenous injection of thorium-B-labelled erythrocytes has been estimated.

The material is rather heterogeneous. Cases with different clinical diagnoses such as hypertension, cerebral hæmorrhage, and cerebral thrombosis are included as well as normal subjects. It has still not been possible to investigate thoroughly the influence of different clinical conditions on the cerebral blood flow. It is, however, our intention to do this in future studies.

The material has been divided into two groups. In Group I (11 cases) injections of thorium-B-labelled erythrocytes in the internal carotid artery have been performed. Simultaneous sampling of blood from both jugular bulbs has been immediately carried out.

In Group II (18 cases), after injection of labelled erythrocytes in an arm vein, simultaneous sampling has been effected from both jugular bulbs and one brachial artery.

Results

Group. I. Injection of thorium-B-labelled erythrocytes in the internal carotid artery and simultaneous blood sampling from both jugular bulbs.

In 7 cases we succeeded in puncturing the jugular bulb on both sides. Thus two dilution curves were obtained simultaneously. In the remaining four cases only one jugular bulb was punctured. The results are to be found in Table I.

The seven cases with samples drawn simultaneously from both bulbs were 2006, 2007, 2015, 2017, 2029, 2030, and 2031. Only in three of these Cases 2007, 2017, and 2029, did we obtain rather similar results for the cerebral blood flow from the two jugular bulbs. In these cases parallel curves from both jugular bulbs are to be found (Fig. 1 and 2). There is a fairly big difference between the values of the cerebral blood flow calculated from the two dilution curves: in Case

TABLE I

CEREBRAL BLOOD FLOW IN 11 CASES DETERMINED BY INTRA-ARTERIAL INJECTION OF THORIUM-B-LABELLED RED CELLS INTO ONE CAROTID ARTERY

Case No.	Dilution curve from jugular bulb	Cerebral blood flow (mean value, litres/min.)		Cerebral pool volume (mean value, litres)		Turnover cerebral blood flow / cerebral pool volume	Total blood volume (litres)	Cerebral pool volume as percentage total blood volume
2001	R		0·50		0·050	10·0	3·120	1·6
2003	R		1·00		0·100	10·0	3·050	3·3
2006a	L	0·57	0·49	0·065	0·057	8·6	4·010	1·4
2006b	R	0·40		0·048				
2015	R	1·20	0·84	0·075	0·062	13·5	3·980	1·7
	L	0·48		0·048				
2017	R	1·00	0·97	0·065	0·066	14·7	4·550	1·5
	L	0·93		0·066				
2032	R		0·80		0·091	8·8	3·460	2·6
2033	R		0·64		0·046	13·9	2·910	1·6
2007	R	1·07	1·02	0·097	0·094	11·0	3·650	2·6
	L	0·97		0·090				
2029	R	1·36	1·25	0·093	0·085	14·7	4·210	2·0
	L	1·14		0·076				
2030	R	0·78	0·92	0·086	0·100	9·2	2·520	4·0
	L	1·05		0·114				
2031	R	0·59	0·80	0·075	0·095	8·4	3·520	2·7
	L	1·02		0·115				
	General mean		0·84		0·077	11·2	3·544	2·3

2007, 100 c.c., i.e. 10 per cent of the mean, in Case 2017, 70 c.c. or 7 per cent, and in Case 2029, 220 c.c. or 18 per cent of the mean. Rather high values of the cerebral blood flow are obtained, viz. 1020 c.c., 970 c.c., and 1250 c.c. respectively. The blood content of the brain (cerebral pool volume) shows a difference between the calculated values, estimated from two venous curves, in Case 2007 of only 7 c.c., i.e. 7 per cent of the mean, in Case 2017 of only 1 c.c. or 2 per cent, and in Case 2029 of 17 c.c. or 20 per cent. The turnover of blood in the brain (i.e. how many times a minute the cerebral blood is changed) is determined at 11 in Case 2007 and at 14·7 in both Case 2017 and Case 2029.

In the other four, namely, Cases 2006, 2015, 2030, and 2031, there are very great differences between the calculated values of the above-mentioned quantities determined from the two dilution curves of the jugular bulbs. For example, the calculated values for the cerebral blood flow differ by 170 c.c. or 35 per cent in Case 2006, 720 c.c. or 86 per cent in Case 2015, 270 c.c. or 30 per cent in Case 2030, and 430 c.c. or 54 per cent in Case 2031. The dilution curves do not run at all parallel in these cases, as is shown in Fig. 3. The maximum of the dilution curve from the right jugular bulb is reached four seconds earlier than the maximum of the curve from the left one. The differences for the calculated pool volumes of the brain are also very high in these cases.

In the four cases where it was possible to puncture only one bulb, we have calculated the cerebral blood flow from only the one dilution curve (Cases 2001, 2003, 2032, and 2033). The cerebral blood flow varies in these cases between 500 c.c. and 1000 c.c. and the pool between 50 and 100 c.c.

We have calculated the general means of the cerebral blood flow and the other quantities mentioned in 11 cases (Table I) and found that the mean of the cerebral blood flow amounts to 840 c.c. and that of the pool volume to 77 c.c. The cerebral turnover is rather high, namely, 11·2, the total blood volume 3544 c.c. and the cerebral blood flow 2·3 per cent of the blood volume on the average. From the dilution curves the circulation time can be estimated, i.e. the time for appearance of labelled erythrocytes in the jugular vein after injection in the carotid artery. It may be difficult to establish the fastest circulation time. The mean circulation time (the maximum of the dilution curve) is easier to determine. The longest circulation time (i.e. the minimum of the dilution

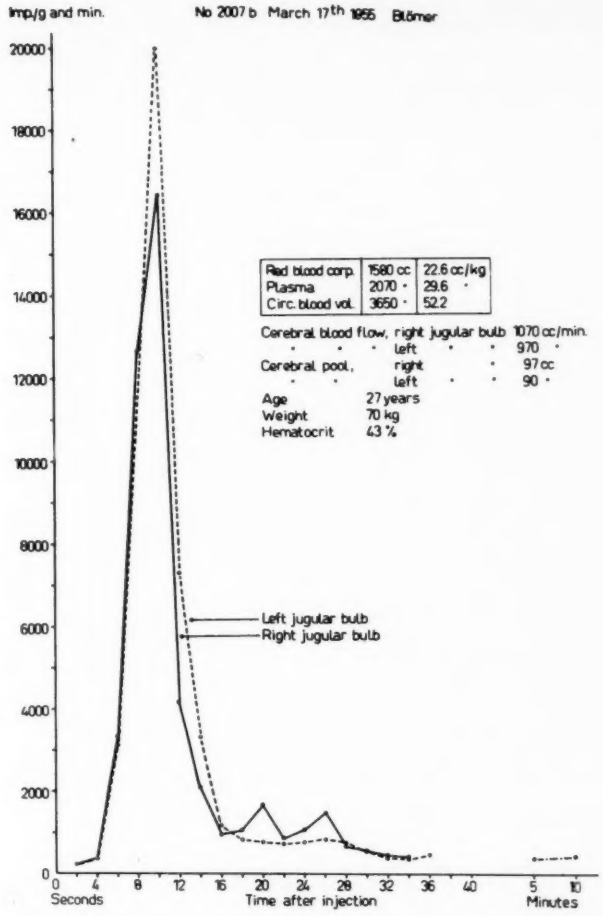

FIG. 1.—Simultaneous dilution curves from the right and left jugular bulbs after injection of thorium-B-labelled red cells into the left carotid artery.

curve) is rather easy to demonstrate. We have found the following means of the three different expressions for circulation time in the brain: shortest time 5·3 sec., maximum 8·9 sec., and disappearance at 18·0 sec. (heterogeneous material).

Group II. Intravenous injection of thorium-B-labelled erythrocytes and simultaneous blood sampling from brachial artery and jugular bulbs.

In 18 cases injections of the labelled erythrocytes were performed in a brachial vein. In 12 cases the blood sampling was made from one brachial artery and one jugular bulb simultaneously. In six cases blood was sampled from both jugular bulbs. It is not possible to calculate the cerebral blood flow and the cerebral pool volume in this way, but dilution curves from both jugular bulbs may give some information about the blood distribution in the two hemispheres. On the other hand, it is possible by sampling from the brachial artery to calculate the cardiac output. This

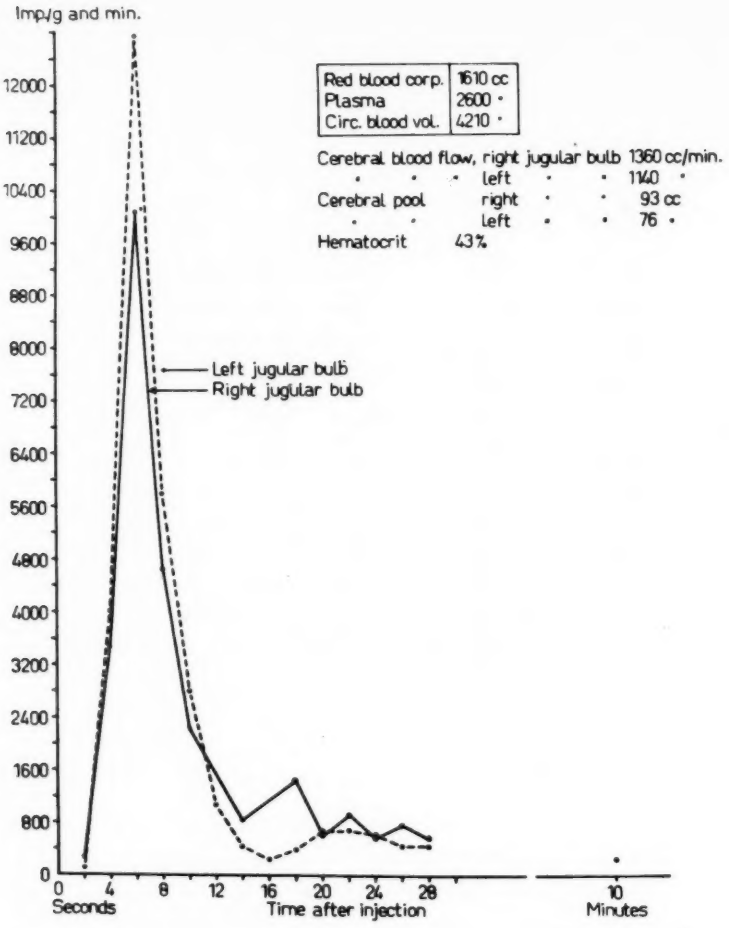

FIG. 2.—Simultaneous dilution curves from the right and left jugular bulbs after injection of thorium-B-labelled red cells into the right internal carotid artery. Case 2029, March 25, 1955, Blömer.

may also be approximately calculated from the dilution curve of the jugular bulb. In Table II are collected the results concerning cardiac output, thoracic pool volume, and also the turnover of blood in the thorax, that is, how many times a minute the thoracic pool is changed. If we compare the cardiac output calculated from the dilution curve obtained from the brachial artery with that of the jugular bulb, it is seen that only in one case (2002) was a notably higher minute volume (+2·6 litres) calculated from the dilution curve obtained from the jugular bulb. In all the other cases the minute volume calculated from the dilution curve of the bulb shows, with an extremely small difference, lower values than that obtained from the brachial artery. There is no significance in the mean difference of the values from the 12 cases. On the other hand, if we exclude the higher value received from the jugular bulb in Case 2002, and then calculate the mean difference between the cardiac output calculated from the dilution curve from the brachial artery and that from the

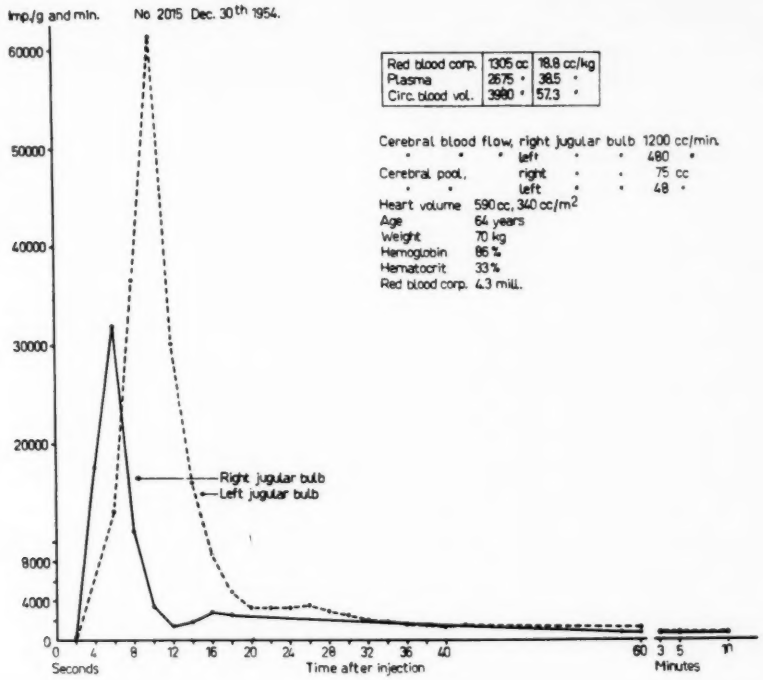

FIG. 3.—Simultaneous dilution curves from right and left jugular bulbs after injection of thorium-B-labelled red cells into the right internal carotid artery.

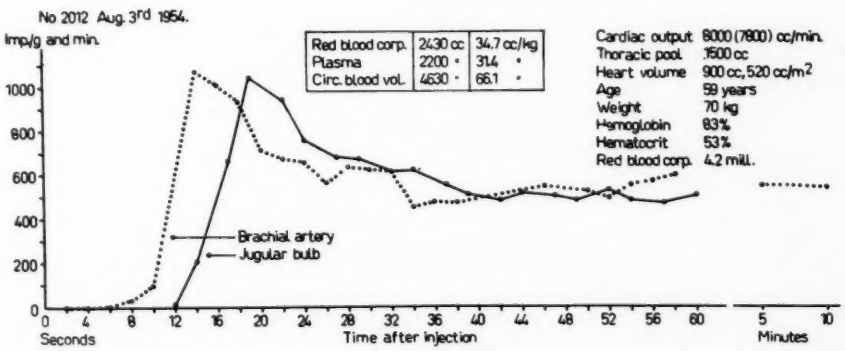

FIG. 4.—Simultaneous dilution curves from the brachial artery and jugular bulb after intravenous injection of thorium-B-labelled red cells.

TABLE II

CARDIAC OUTPUT CALCULATED FROM SIMULTANEOUS DILUTION CURVES FROM BRACHIAL ARTERY AND JUGULAR BULB

Case No.	Dilution curve from	Cardiac output (l./min.)	Thoracic pool volume (litres)	Turnover cardiac output thoracic pool	Total blood volume (litres)	Thoracic pool as % of total blood	Heart volume	
							litres	l./m.²
2011	Brachial artery	8·6	1·13	7·6	3·18	35·6		
	R jug. bulb	8·4						
2002	Brachial artery	6·0	1·56	3·9	4·43	35·2		
	R jug. bulb	8·6						
2000	Brachial artery	8·0	1·34	6·0	3·56	37·6		
	R jug. bulb	7·9						
2012	Brachial artery	8·0	1·50	5·3	4·63	32·4	0·91	0·52
	R jug. bulb	7·8						
2013	Brachial artery	5·2	1·08	4·8	4·18	25·8	0·62	0·37
	R jug. bulb	5·1						
2004	Brachial artery	8·4	1·08	7·8	3·83	28·2	0·57	0·34
	R jug. bulb	8·4						
2005a	R and L jug. bulbs	5·2						
2005b	R and L jug. bulbs	5·0			4·77			
2016	R jug. bulb	9·0						
	L jug. bulb	7·8			4·25			
2036	R jug. bulb	3·8			3·88			
2020	Brachial artery	5·9	1·62	3·6	3·94	41·1		
	Jug. bulb	5·3						
2021	Brachial artery	8·2	0·98	8·4	3·56	27·5	0·67	0·38
	Jug. bulb	8·1						
2022	Brachial artery	4·1	0·70	5·9	3·18	22·0	0·70	0·41
	R jug. bulb	3·7						
2008	Brachial artery	9·1	1·08	8·6	3·18	33·4	0·55	0·37
	R jug. bulb	8·9						
	L jug. bulb	8·6						
2026	R and L jug. bulbs	7·5			3·84			
2027	R jug. bulb	5·2			3·72			
	L jug. bulb	5·1						
2034	R jug. bulb	3·4			2·24			
2028	Femoral artery	5·8	1·05	5·5	2·92	36·0		
	R jug. bulb	5·2						
2035	R jug. bulb	10·8			4·74			
	General mean	7·03	1·19	6·1	3·78	32·3	0·67	0·40

Mean values calculated from brachial artery.

jugular bulb, we find the difference to be 236 c.c. As a proportion of the minute volume of the heart this difference amounts to only 3·3 per cent.

The thoracic pool has been determined from the brachial dilution curve of the brachial arterial blood in 11 cases and varies rather inconsiderably among the individual cases. The general mean amounts to 1·19 litre.

The turnover of the thoracic pool is calculated at 6·1 per minute. The thoracic pool as a percentage of the total blood volume is determined at 32 per cent. Not all cases have had their heart volume examined, but in the six cases where this has been done the heart volume had normal values. Fig. 4, 5, and 6 show how similar the dilution curves from the brachial artery and those of the jugular bulb prove to be. Fig. 6 shows simultaneous dilution curves obtained from the brachial artery and both jugular bulbs. It is striking in this case that the two dilution curves from the veins run parallel and give the same values of the cardiac output and that about the same value is calculated from the dilution curve from the brachial artery. As in our first publication, however, we have found that the dilution curves from the two jugular bulbs differ in some cases; one example is given in Fig. 7. It is probable that this fact explains the rather great difference between the cardiac output calculated from these two curves. The time difference for the maximum

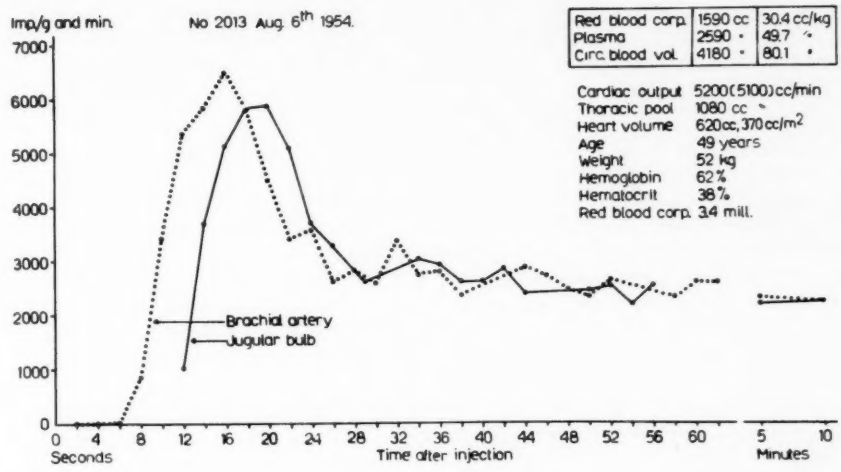

FIG. 5.—Simultaneous dilution curves from the brachial artery and jugular bulb after intravenous injection of thorium-B-labelled red cells.

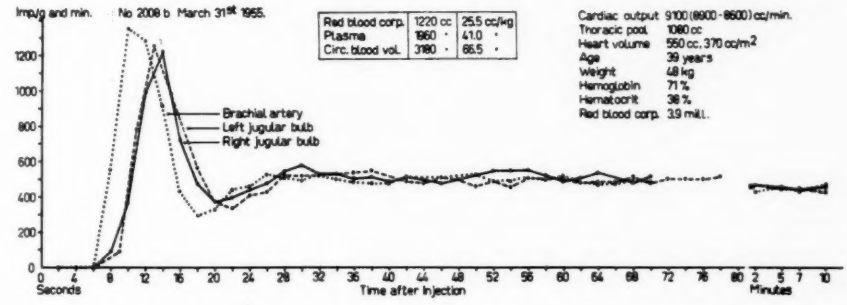

FIG. 6.—Simultaneous dilution curves from the brachial artery and both jugular bulbs after intravenous injection of thorium-B-labelled red cells.

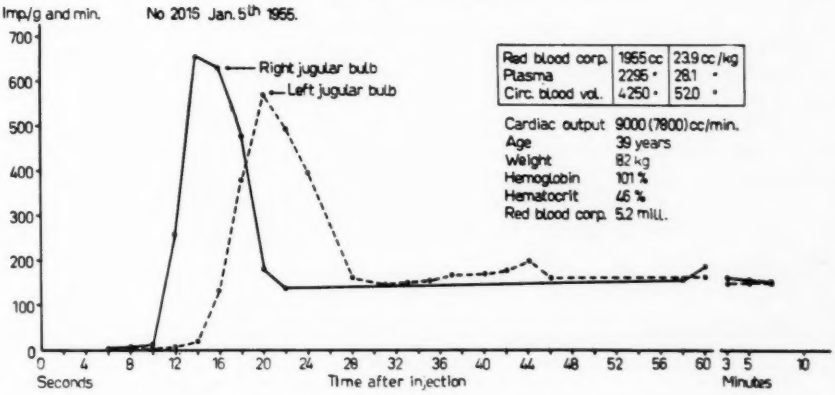

FIG. 7.—Simultaneous dilution curves from both jugular bulbs after intravenous injection of thorium-B-labelled red cells.

of the two dilution curves amounts to no less than 6 sec. If we compare the mean of 840 c.c. of the cerebral blood flow in Table I with the mean of 7030 c.c. of the cardiac output in Table II, we find that the cerebral blood flow is 12 per cent. of the cardiac output.

Discussion of the Results

The question arises whether the dilution curve from the jugular bulbs really represents, at least in normal conditions, a mixing curve of all the blood in the brain independently of whether the injection of the blood has been done through one or both carotids or through the vertebral arteries. The arterial anastomoses in the brain and especially the big venous sinuses probably support the assumption that the blood received from the jugular bulb is mixed with all the blood in the brain, at least in normal conditions. One would expect to receive parallel dilution curves from the two veins. Our determinations on the cerebral pool seem to show that the brain contains astonishingly small quantities of blood—about 80 c.c. or only 2 per cent of the total blood volume. The remarkable fact in our results is that the cardiac output, whether calculated from the dilution curves from the brachial artery or from the jugular bulbs, has the same value. This would probably not happen if there was not complete mixing with a rather small quantity of blood in the brain. As has been mentioned before, our material does not consist of uniform normal cases, and pathological cases are included in it. It is our intention to get a larger group which could be divided into normal and pathological cases. Therefore this paper also must be regarded as a preliminary report. As a probable example of unequal distribution of blood in the brain we have Case 2016 (Fig. 7), where the two simultaneous dilution curves do not run parallel and have strikingly different values for the cardiac output. Why this is so we cannot yet tell. Probably the same happens in Case 2015 (Fig. 3). Mostly we have obtained parallel dilution curves from both jugular bulbs whether, as in Cases 2007 and 2029, after intracarotid injection or as in Cases 2008 (Fig. 6), 2027, and 2026 after intravenous injection. These results also speak in favour of the assumption that there has been complete mixing of the blood in the brain. Our studies, even though only preliminary, have, we feel, made a contribution to our knowledge concerning the mixing and distribution of blood in the brain that may be of practical importance in clinical conditions.

If we are right in assuming that complete mixing between the injected substance and all the blood in the brain occurs, the calculation of the cerebral blood flow is probably correct and the value of 840 c.c. for the mean cerebral blood flow would be reasonable and constitute 12 per cent of the cardiac output—a quantity more acceptable than the 20 per cent that has previously been assumed.

Summary and Conclusions

With increasing experience of our method we have continued our study of the cerebral blood flow by means of thorium-B-labelled erythrocytes.

If parallel curves from both jugular bulbs are obtained it is probable that complete mixing has taken place with all the blood in the brain. Differences between them may be of clinical importance.

The values of the cerebral blood flow are absolute values and not relative ones as are those obtained by the nitrous oxide gas method.

The cerebral blood flow has been determined, the mean value being 0·84 litre or about 12 per cent of the cardiac output.

The cerebral pool volume (the content of blood in the brain) is found to be 77 c.c., only 2 per cent of the total blood volume, a figure that has not hitherto been determined.

The turnover of blood in the brain is 11·2 per minute or twice that in the thorax, which has a value of 6·1.

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TWO MORE FAMILIES WITH CARDIOMEGALY

BY

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When the well-recognized causes of cardiac hypertrophy have been excluded there is still a group of patients in whom large hearts are found: the diagnosis may have been made on routine examination or following the investigation of cardiac failure or arrhythmia. Elster *et al.* (1955) gave clinical and post-mortem details of ten cases of rapidly fatal cardiac failure associated with a large heart, and discussed the possible ætiology.

A familial incidence of cardiac enlargement has not, however, been reported often. It is known to occur in von Gierke's disease and in Friedreich's ataxia, both of which have a familial incidence. In von Gierke's disease the condition is always associated with disturbances of carbohydrate metabolism and usually with hepatomegaly, and is almost invariably diagnosed in childhood. Occasionally the heart alone is affected (Pompe, 1932): it becomes large, partial or complete heart block often developes, and cardiac failure may be the cause of death. Histological study reveals glycogen deposits in the myocardium (von Gierke, 1929; Ellis and Payne, 1936).

In Friedreich's ataxia, Evans and Wright (1942) found striking electrocardiographic abnormality in 12 of 38 patients with neurological features. It was more common to find the heart involved in those with a family history of the disease. Cardiac enlargement was not evident clinically though it could be demonstrated on fluoroscopy; there was complete heart block in two patients and flattening or inversion of the T waves in the limb leads in nine. Histological examination of the myocardium showed muscle fibre hypertrophy with patchy fibrosis, and the Purkinje fibres also were separated by fibrous tissue (Russell, 1946). We have not found among the families with Friedreich's ataxia any members who show cardiac involvement only without neurological features.

There remains a group of patients showing a familial incidence of cardiac enlargement with arrhythmia but without associated disease. Evans (1949) reported nine cases with cardiomegaly of unknown ætiology, of which three occurred in one family and two in another, and four were isolated cases. In four of the five familial cases cardiac disease was not discovered until adult life. The enlargement of the heart was chiefly due to the left ventricle, the blood pressure was always normal, and a triple rhythm was frequently heard. The changes of rhythm included paroxysmal tachycardia, auricular fibrillation and flutter, and atrio-ventricular and bundle-branch block. Two patients died, two months and four years after the onset of syncopal attacks. Histological examination revealed great hypertrophy of the muscle fibres of the myocardium with interstitial fibrosis, but without gross cellular infiltration or any fatty replacement of muscle fibres: although glycogen was found in one instance, Evans thought that these were not cases of van Gierke's disease.

We have not been able to find reports of many other families similarly affected, though one has been described by Gaunt and Lecutier (1956). The condition of the heart in the family reported by Paulley *et al.* (1956) was attributed to toxoplasmosis, but this was not certain.

The condition is sufficiently uncommon to warrant this account of two families: the first includes a mother and son only though many others had died early in life; in the second a slow heart rate, due to heart block in two members and to sinus bradycardia with bundle-branch block in the third, is known to have been present in three generations, and other members of the family had some evidence of cardiac abnormality and two died at an early age.

The First Family

Case 1, aged 23, at death. A. D. was thought to have rheumatic fever when he was 7 and was not allowed to play games at school, but led a normal life otherwise. When 17, he was rejected for the navy because of his heart, but had no symptoms until he was 20, since when he had noticed palpitation on exertion and at other times had felt faint, and had lost consciousness once. During the next two years he became increasingly short of breath, until he could climb only one flight of stairs. He had also had about eight attacks of severe præcordial pain, often associated with the spells of dizziness or palpitation; these usually lasted half an hour, but one early attack that was unusually severe lasted all night and needed morphia for its relief. The pain did not seem like that of coronary ischæmia, but this could not be excluded with certainty at the time (see necropsy).

On examination, he had no cyanosis or dyspnœa at rest. The pulse was regular except for ventricular extrasystoles. There was no thrill, but a soft systolic murmur in the mitral area that was not thought indicative of any valvular disease; the second sound in the pulmonary area was widely split. The apex beat was near the anterior axillary line, and the heart was globular and very large, especially the left ventricle: unfortunately the film has been lost. His blood pressure was low, 90/55. The cardiogram showed left bundle-branch block with a QRS width of 0·18 sec. and high voltage in V3 (Fig. 1). The P wave was

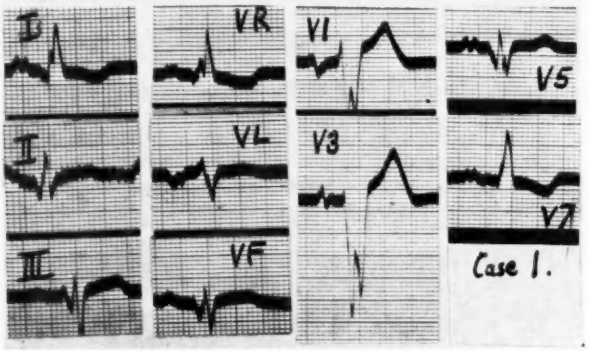


Fig. 1.—Electrocardiogram of Case 1 a year before his death, showing left bundle-branch block.

notched and bifid and the P–R interval was 0·24 sec. His hæmoglobin was 110 per cent with a red blood count of 5·7 million. After a period of rest in hospital he returned to work.

Some months later he was admitted into the West London Hospital under Dr. G. L. S. Konstam, under whose care he had been earlier, and died in a prolonged paroxysm of tachycardia. Dr. Konstam has informed us that his case was reported by Blanshard (1953) with an account of the necropsy which we have therefore abridged.

Necropsy. The heart weighed 820 g.: it was pale with many petechial hæmorrhages. Both ventricles were enlarged, the wall of the right being 5 mm. thick compared with the enormously hypertrophied left ventricle which was 25 mm. thick. There was fibrosis towards the apex anteriorly and a fibrous patch 25 by 12 mm. in the wall of the right ventricle, and diffuse fibrosis in the lower part of the septum. The mitral valve was normal with some roughening on the margin. The other valves were normal. The coronary arteries were normal but small compared with the massive left ventricle. The lungs were congested with patches of broncho-pneumonia. The liver was congested with nutmeg changes. The spleen weighed 370 g. There were no other abnormalities.

On microscopical examination, the muscle fibres were hypertrophied and there was dense patchy fibrosis of the myocardium in all the parts examined; no Aschoff bodies were seen. There was scattered cellular infiltrate consisting of lymphocytes and mononuclear cells (Fig. 2, Blanshard, 1953). The sections were examined by Dr. Harrison and his views are quoted in the discussion.

Case 2, aged 29 at death. G.D., the mother of Case 1, her only child, had been in the National Heart Hospital under Dr. Parsons-Smith eighteen years before. She was thought to have had rheumatic fever

when she was 15 and was in bed for five months. Nevertheless, she led an active life, doing all her housework without symptoms, until a rather sudden onset of dyspnœa when she was 28, followed quickly by congestive failure two months before admission. She had a large globular heart (c.t.r. 68%) that seemed to involve all chambers, the left more than the right (Fig. 2). She had a double second sound that was thudding in character, and was thought to have mitral stenosis though a faint diastolic murmur was heard only irregularly and the systolic murmur was not loud. Her blood pressure was 105/68. She had an even more remarkable picture of bundle-branch block with a QRS of 0·18 sec. (Fig. 3). Her Wassermann reaction was negative.

After leaving hospital she got on all right for a year when she was readmitted with the same symptoms and severe giddiness. The signs were as before except that the heart was even larger (c.t.r. 71%) and the cardiogram of lower voltage with the QRS width increased to 0·22 sec. (Fig. 3). Again she responded to treatment and seemed fairly well, but died, aged 29, quite suddenly while being examined two days before she was due to go home. Unfortunately there was no necropsy.

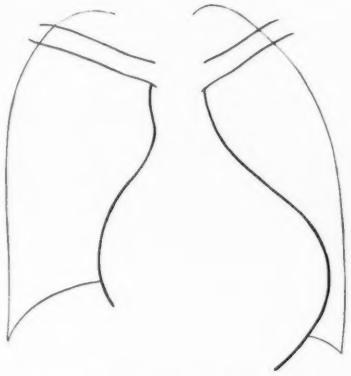


FIG. 2.—Orthodiagram of the heart of Case 2, showing great enlargement with a cardiothoracic ratio of 68 per cent.

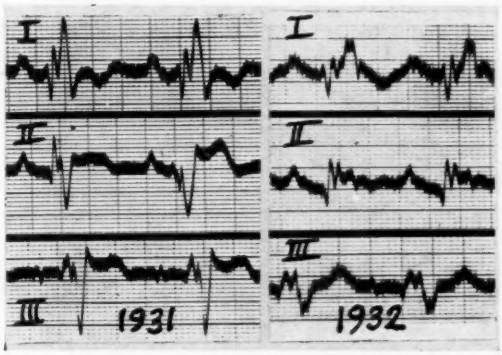


FIG. 3.—Standard lead electrocardiograms from Case 2, showing bundle-branch block with widening QRS complexes, in 1931 a year before, and in 1932 just before, her sudden death.

Other Members of the Family. When Case 1 was in hospital, only one of the twelve brothers and sisters of his mother (Case 2) was still living. Blanshard (1953) states that 8 of these 12 had died with heart disease, four between the ages and 23 and 40 and four in infancy: he does not seem to have been aware of the death of Case 2, possibly because when Case 1 was in hospital all references to her were avoided, as we were so impressed by the resemblance of the two and so fearful that Case 1 would die suddenly as his mother had.

The father and mother of Case 2 had lived to 76 and 78 and had no history of heart disease, but an aunt was said to have dropped dead in the street when she was 19 years of age.

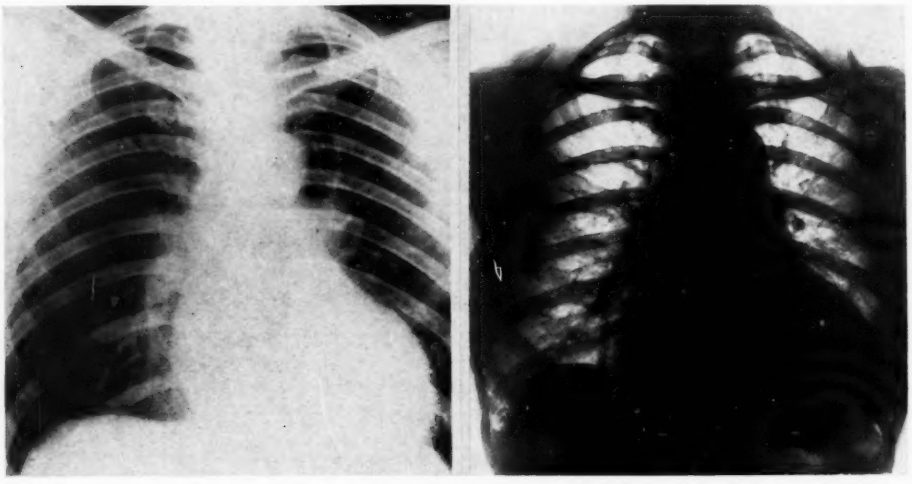
THE SECOND FAMILY

Case 3, aged 36 at death. A. M. had jaundice at the age of 17, and was seen by one of us with his mother (Case 4): no cardiovascular abnormality was found. He continued to lead a full and active life, playing rugger for his public school and while in the army. He had dysentery three times, but no other serious illnesses.

In 1950, when he was 36, he was admitted to University College Hospital under the care of Dr. J. C. Hawksley, complaining of attacks of unconsciousness for three months. His first attack came while he was sitting down, and he gave a vivid description of a feeling like a blush spreading upward over his body followed by profuse sweating; he then became dizzy and unable to think clearly, and finally fell to the ground unconscious. During the next three months he had three similar attacks, each lasting a few minutes.

On examination, he was intelligent and well built. His pulse was regular at 40 a minute and the blood pressure was 128/70. There were no signs of congestive failure either on admission or later. The heart

sounds were normal; there were no murmurs and no triple rhythm. The apex beat was 11·5 cm. from the mid-line and thrusting in quality: X-ray examination showed a large heart, especially the left ventricle, the cardiothoracic ratio being 55 per cent (Fig. 4A). The liver and spleen were not palpable, and there were no neurological or skeletal abnormalities. The hæmoglobin was 98 per cent, the blood count normal, and



A B

FIG. 4.—Teleradiograms, showing enlargement, especially of the left ventricle. (A) Case 3. The cardiothoracic ratio was only 55 per cent but the heart weighed 1050 grammes. (B) Case 4, aged 66, the mother of Case 3. A very large heart with a cardiothoracic ratio of 62 per cent (17/27·6 cm.). Although she now has hypertension with a blood pressure of 200/100 we think that most of the enlargement is due to the myocardial changes as the blood pressure was still 140/80 when she was 60, in 1950.

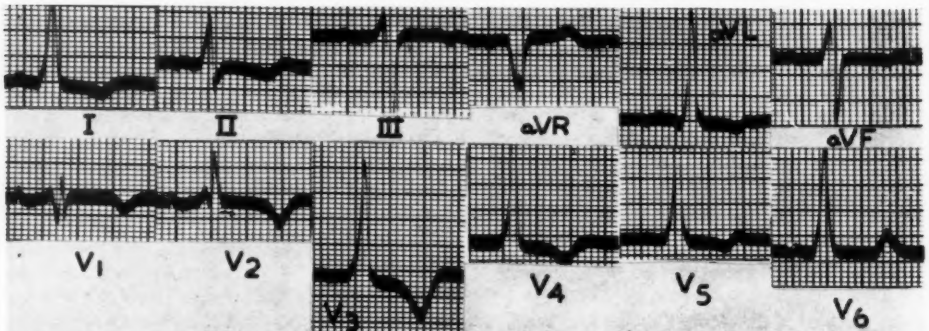


FIG. 5.—Electrocardiogram between attacks. Rate 35 a minute. Sinus rhythm. Left axis deviation. T wave inversion maximal in V3. Case 3 (7/10/50).

the sedimentation rate 14 mm. in an hour. The Wassermann and Kahn reactions were negative as they had been in 1932.

Between attacks he showed either a sinus or nodal bradycardia, and during attacks of faintness, varying high degrees of A-V block, sometimes complete. On admission there was sinus bradycardia at 35 a minute with occasional nodal and ventricular extrasystoles. There was left axis deviation, a small W complex in V1, and inverted T waves maximal in V3 (P–R, 0·2 sec. and QRS, 0·12 sec.) (Fig. 5), and later there was

nodal rhythm with complete left bundle-branch block (Fig. 6B). During the first attack of faintness recorded there was an idiopathic ventricular rhythm at a rate of 35 a minute (Fig. 6A). During some later attacks the ventricular rate fell to about 12 a minute, due to a high degree of A-V block (8:1), the atrial rate being 100 a minute (Fig. 6C). During another attack an atrial rate of 35 a minute with 2:1 A-V block was observed (Fig. 6D).

The onset of bradycardia between 8 and 10 beats a minute was sudden and lasted about thirty minutes. The recovery to a rate of about 50 a minute took place gradually over a period of fifteen minutes; occasionally, but much less often, there was sudden doubling or halving of the rate. The syncopal attacks which were often accompanied by pain increased in frequency and severity until the fatal one two months after his admission. Intravenous atropine was given to relieve them, but tended to induce A-V block. Intramuscular ephedrine had no effect on the heart rate. The fatal syncopal attack had lasted thirty minutes

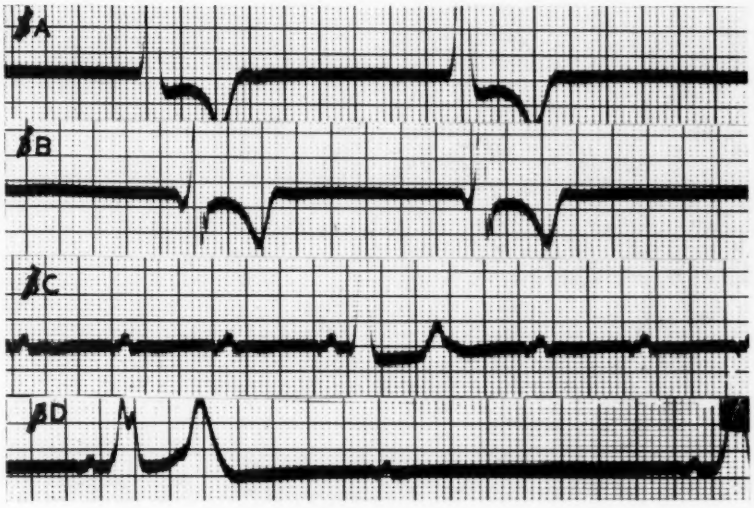


FIG. 6.—Electrocardiograms (lead II) during and between attacks. (A) During an attack. Recording considered to represent idiopathic ventricular rhythm at a regular rate of 35 a minute with complete heart block (9/10/50). (B) Between attacks. Nodal bradycardia, rate 39 a minute. P inverted and P–R of 0·1 sec. (21/11/50). (C) During attack. Atrial rate 94 a minute. A longer strip of this recording showed 6:1 and 8:1 A-V block (22/11/50). (D) During attack. Sinus bradycardia, atrial rate 37 a minute with 2:1 A-V block (22/11/50). Case 3.

when the heart stopped beating and neither intravenous coramine nor subcutaneous and intracardiac adrenaline were of any avail.

Necropsy. The heart weighed 1050 g. The pericardium over the right atrium showed thickening due to old pericarditis. The gross enlargement was chiefly due to the massive left ventricle, the walls of which exceeded 25 mm. in thickness (Fig. 7). The endocardium and valves were normal, and there was no evidence of rheumatic disease. The atrial walls were thickened. The sinu-atrial node was visible through the endocardium as a yellowish mass, and the atrio-ventricular node was similarly represented although not visible except on the cut surface. The coronary vessels showed some medial thickening, but no narrowing; they were, however, disproportionately small in relation to the enormous ventricle (cf. Case 1).

Histology. The left ventricular myocardial fibres were hypertrophied; some showed central clear spaces and some œdema, but there was no fatty change or fibrosis. Central clear spaces were present also in the hypertrophied atrial muscle; these were not globular as in fat, nor basophilic as in glycogen. Most of the atrial hydropic fibres were devoid of nuclei (Fig. 8). Fibres in the S-A and A-V nodes were grossly hydropic and lay in interstitial fat and fibrous tissue. A hyalinized scar was also present in the A-V node. The hydropic areas contained no substance that could be identified by the usual histochemical methods:

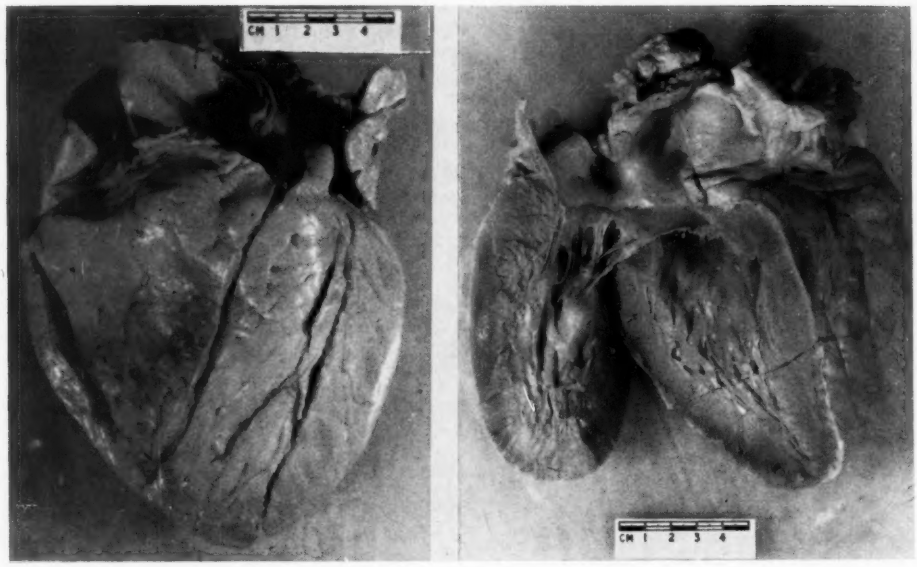


FIG. 7.—Macroscopic appearance of the heart that weighed 1050 grammes. The mitral valve was normal at necropsy but was torn during dissection. Case 3.

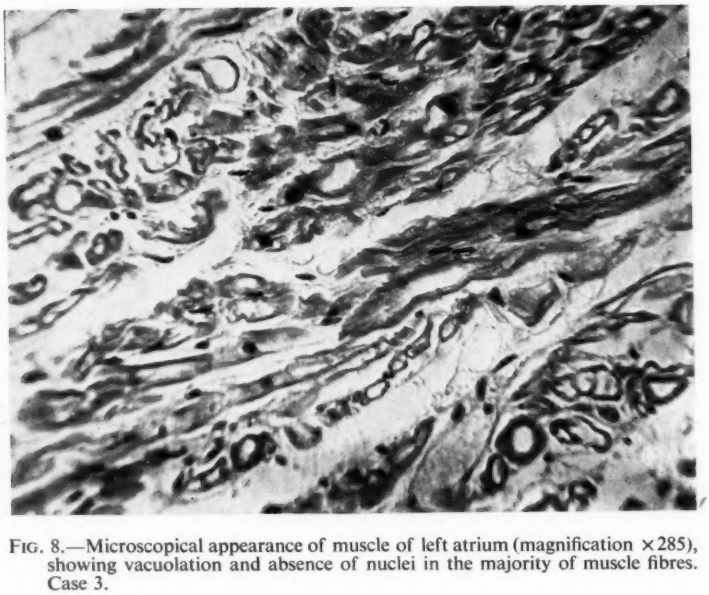


FIG. 8.—Microscopical appearance of muscle of left atrium (magnification ×285), showing vacuolation and absence of nuclei in the majority of muscle fibres. Case 3.

no glycogen could be demonstrated by the periodic acid Schiff reaction, and the only fat demonstrated by Scharlach red lay in the fat cells between the distorted muscle fibres.

The Children of Case 3. His two children, a boy now aged 10 and a girl aged 7, were examined in 1950: the boy was found to have an apical systolic murmur and radiographic evidence of slight enlargement of the heart, but no abnormality was found in the girl. Both children have been examined again in 1956 and show no clinical, radiographic, or electrocardiographic evidence of heart disease.

Case 4, now aged 66. G. M. gave no history of rheumatic fever. When she was 23, her only child (Case 3) was born. About three years later she began to feel tired and breathless and had attacks of faintness though she was rarely unconscious. Her doctor found she had a slow pulse, generally 45–50, but once as slow as 25 a minute.

She was first seen by one of us in 1928 when she was 38 and there was little change in her condition during the next ten years. She had to lead a quiet life and suffered from faintness and extreme fatigue if she did too much, and was always too breathless to lead the active life she had led till she was 25 years old. Treatment with thyroid did not help her and there was no suggestion of myxœdema. The position and force of the apex beat suggested a larger heart than the cardiothoracic ratio of 53 per cent (cf. Case 3). There was a systolic murmur at the apex which was constant and widely conducted; mitral regurgitation was suspected, but no diastolic murmur nor any other evidence of mitral stenosis was found. Her blood pressure was about 140/80.

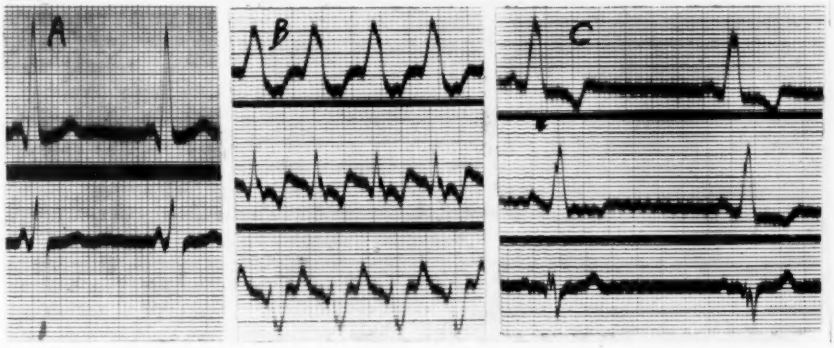


FIG. 9.—Electrocardiograms of Case 4. (A) Leads I and III in 1929; (B) auricular flutter with 2:1 block in 1940; and (C) sinus bradycardia and bundle-branch block later in 1940.

During these ten years her heart rate was between 32 and 60, most often between 40 and 48 a minute, and she felt better when it was faster and often felt faint when it was slower. The electrocardiogram showed sinus bradycardia (range 40–60) with sinus arrhythmia and occasional ventricular extrasystoles, and left axis deviation with no inversion of the T waves (Fig. 9A). The short P–R interval, 0·11 sec., and the wide QRS, 0·11 sec. and sometimes 0·14 sec., suggested the Wolff-Parkinson-White syndrome, but in 1937 when for the first time in a dozen records the P–R interval was 0·16 sec., QRS was equally wide.

In 1940 she was admitted with paroxysmal tachycardia at a rate of 150 a minute, probably auricular flutter with 2:1 block (Fig. 9B), which stopped on the fifth day after 3 drachms of digitalis in four days. For the next three weeks her pulse was charted generally between 32 and 48 a minute, and a cardiogram showed sinus bradycardia at 40 a minute with a P–R interval of 0·20 sec. and left bundle-branch block (QRS 0·14 sec.); T was inverted in lead I for the first time (Fig. 9C).

She was seen again in 1945 and in 1950 and had been getting on well except for six further paroxysms of tachycardia, two lasting for three and five days. The physical signs and heart rate were unchanged but the heart was larger. In 1945 T1 was again upright, but in 1950 there was classical left bundle-branch block with T inversion in leads I and V7 (QRS, 0·16 sec.; Fig. 10).

She is now 66 and is not much changed, except that her blood pressure has risen from 140/80 to 220/110. The rate is generally about 40–50 a minute and the systolic murmur and bundle-branch block are as before, but the heart has become larger (Fig. 4B): we do not attribute much of the increase to the high blood pressure as this was still 140/80 in 1950.

FIG. 10.—Standard and unipolar leads from Case 4 in 1950. There has been no significant change between 1950 and 1956.

Note on the Husband of Case 4. Three years after Case 4 was first seen, her husband was found to have syphilitic aortic incompetence and he died with heart failure three years later. There was nothing to suggest that the heart lesion of Case 4 was syphilitic and her Wassermann and Kahn reactions were negative both in 1932 and in 1940, and this was also true of their son (Case 3). In view of these negative findings and the absence of any evidence of syphilis in the necropsy of Case 3, it is unlikely that this played any part.

Case 5. One of three sisters of Case 4, had lone auricular fibrillation that reverted to normal within 17 days. Nothing else abnormal was found about her heart so this may be no more than a chance finding.

Earlier Generations. Case 6. The mother of Cases 4 and 5 lived till she was 69 but suffered with her heart for several years and the diagnosis on the death certificate was " heart failure and complete heart block "; we do not know how long the heart block had been present.

Three of her sisters were said to have had heart disease. Two lived to 70 and 84, but the former had been an invalid for years and was said to have a slow heart: the third is said to have died before she was 20 with heart disease; she was in Guy's Hospital as a girl in 1880, but the notes are not available and she was indexed as disease of the spine.

In the previous generation, the mother of Case 6 died, also with heart disease, while she was still in her thirties; she was said to have been in Guy's Hospital, but we have been unable to find the case notes. We have no proof that these members of earlier generations suffered from the same heart condition but it is likely: heart block, slow heart rates, and early deaths without evidence of rheumatic heart disease were more frequent than would be expected.

DISCUSSION

In our first family a mother and son, both with very large hearts and bundle-branch block, died suddenly at an early age, one year and three years respectively after the onset of symptoms. In our second family a young man (Case 3) and his maternal grandmother had heart block and his mother (Case 4) had sinus bradycardia and bundle-branch block. The duration of symptoms in the grandmother is not known: in the mother they started when she was 28 and still persist 38 years later, but the son died suddenly at the age of 36, within five months of his first Stokes-Adams attack.

Cases 3 and 4 demonstrate the extreme variability of survival times, irrespective of the initial cardiographic and radiological findings: early and sudden death is more usual, as in most of the

cases reported by Evans (1949) who suggested that the prognosis was poor when major cardiographic changes and a large heart were present in a young person.

Hearts weighing over 1000 grammes are relatively uncommon in any condition, but the heart weighed 1134 g. in Case 1 of Evans, 1050 g. in our Case 3, 820 g. in our Case 1, and 737 g. in Case 1 of Gaunt and Lecutier.

Among the cases reported by Evans (1949) and by Gaunt and Lecutier (1956) extrasystoles, paroxysmal tachycardia, auricular fibrillation, bradycardia, heart block, and bundle-branch block were all fairly common, and both these authors stress the high voltage of the QRS complexes, as in some of our cases. Bradycardia seemed common among the cases reported by Evans and heart block was present in Case 1 of Gaunt and Lecutier and from time to time in their Case 3, who had Stokes-Adams attacks. It seems likely that our Case 5 suffered from the same familial disorder as no other cause for auricular fibrillation was found, but it may have been fortuitous.

There was no evidence of any of the neurological features of Friedreich's ataxia in any members of these families, but few of them were specifically examined.

The ætiology of this condition remains obscure in spite of the histological data available. A diffuse degenerative process affecting the entire thickness of the myocardium appears to be the fundamental lesion: the muscle fibres are hypertrophied but the most striking feature is the vacuolation of muscle fibres and of the conducting system. The histological picture in our Case 3 differs from that described by Evans (1949) in that fibrous tissue is almost completely absent and the hydropic change is greater. This vacuolation of the muscle fibres was also a main feature in the necropsy of Gaunt and Lecutier (1956). Patchy fibrosis was, however, present in our Case 1 and the sections were examined by Dr. C. V. Harrison who reported " This is an example of smouldering almost healed myocarditis. The fibrosis is not of the type or distribution that one sees in either rheumatism or ischæmia and there is endarteritis in small arteries and still some cellular infiltration in the interstitial tissue." It was for this reason that the case was reported (Blanshard, 1953) as one of isolated diffuse myocarditis, but we think this diagnosis pays too little attention to the clinical picture and family history.

There is no evidence of endocarditis or of myocardial changes suggestive of rheumatic disease. The distribution of the lesions is unlike that described in subendocardial fibrosis (Gray, 1951). Although there is medial thickening of the coronary arteries, coronary occlusion is not demonstrated and the myocardial changes are disproportionately great. Cellular infiltration of the isolated myocardium is generally minimal and unlike the typical findings in isolated myocarditis or in cardiovascular collagenosis (Becker *et al.*, 1953).

Glycogen could not be demonstrated by the periodic Schiff technique in any part of the heart of Case 3. The necropsy was performed 24 hours after death and the left ventricle was fixed unopened, two factors that might account for loss of glycogen before staining; but the right ventricle was opened at the necropsy and fixation was rapid so glycogen should have been demonstrated had it been present. Glycogen storage disease affecting the heart alone has been reported (Pompe, 1932; Abbott, 1909; von Crevald and van der Linde, 1939) but all the patients have died within the first four years of life.

Though familial cardiomegaly is generally unnoticed till early adult life it seems more likely that there is a genetic cause. The evidence is scanty but suggestive of its inheritance as a dominant Mendelian character.

Summary

Two more families with cardiomegaly unassociated with any other familial disease are reported. In one a mother and son died young with very large hearts and bundle-branch block. In the other, three members in three generations had large hearts and a slow heart rate, two with heart block and the third with sinus bradycardia and bundle-branch block. None of the accepted causes of cardiac enlargement was present. Several other members of both families died at an early age or had a history of heart disease.

Although familial cardiomegaly is generally associated with early death, one of our patients is still living at the age of 66 years.

The morbid anatomy and histology of two cases are described.

We are greatly indebted to Dr. Geoffrey Konstam for giving us the information about the necropsy of Case 1 and about the report of this case by Blanshard.

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SPECTRAL PHONOCARDIOGRAPHIC STUDIES IN CONGENITAL HEART DISEASE

BY

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The principles and technique of spectral phonocardiography have been described in detail in earlier publications from this laboratory (McKusick *et al.*, 1954). The method provides detailed frequency-time-intensity plots of cardiovascular sound. It resembles in some respects the manner of operation of the auditory mechanism on these sounds. In essence the spectral phonocardiogram is made up of a large number of horizontal lines, each representing the output of an individual pass-band filter. In other words, in making the spectral phonocardiogram a selected segment of sound (in electrical form) is in effect put through a battery of a very large number of individual electrical filters each of which is tuned to a specific and different, although overlapping, pass-band.

Spectral phonocardiography has the following advantages over conventional oscillographic phonocardiography (McKusick *et al.*, 1955): (1) resolution in the time dimension is improved; (2) the wide intensity range of cardiovascular sound is better encompassed with simultaneous display of faint and loud components in their true proportions; (3) quality (timbre) is represented accurately; and (4) vibrations of non-cardiovascular origin are more easily identified. Spectral phonocardiography can do, or at least can be made to do, all the ear can. It can exceed the performance of the ear because (1) resolution in the time dimension is better, (2) it is not wed to one particular frequency response curve, (3) it is not handicapped by psycho-acoustic phenomena such as masking, and (4) permanent, quantifiable records are produced.

METHODS

Simultaneous recordings of heart sounds, electrocardiogram, and respiratory phase tracing were made on magnetic tape. The electrocardiogram and respiratory mark were recorded by means of frequency modulated carriers. A microphone (Altec 21–BR–150) of the condenser type was employed for pickup and transducing purposes. As a rule, quiet respiration was permitted during the recordings which were routinely made at the aortic area, at the pulmonary area, at the lower left sternal border (4th interspace), and at the apex. The tape recordings, raw data for the studies, were audited and selected sections analysed on the modified Bell sound spectrograph. In the spectral phonocardiogram the *time* dimension is on the *abscissa* as in most physiological recordings. The *ordinate* is *frequency* spectrum, not intensity. *Intensity* is represented by the *degree of blackness* of any given portion of the recording.

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The subject material consisted of approximately 100 patients with many varieties of congenital heart disease admitted principally to the Surgical Service of The Johns Hopkins Hospital for cardiac catheterization and/or surgical intervention. Atrial septal defect and pulmonary stenosis are the largest single diagnostic categories studied. Discussed here are the findings in these cases and in primary pulmonary hypertension, thoracic arteriovenous fistula, and congenital mitral stenosis.

Pure Pulmonary Stenosis, Valvular Type

The systolic murmur in these cases has had a Christmas tree appearance as in the case of the systolic murmur of aortic stenosis. Usually the frequency and intensity peak has been later in systole than in the murmur of aortic stenosis. In fact, its peak is at times so late in systole that the murmur has almost a crescendo construction (Fig. 1).

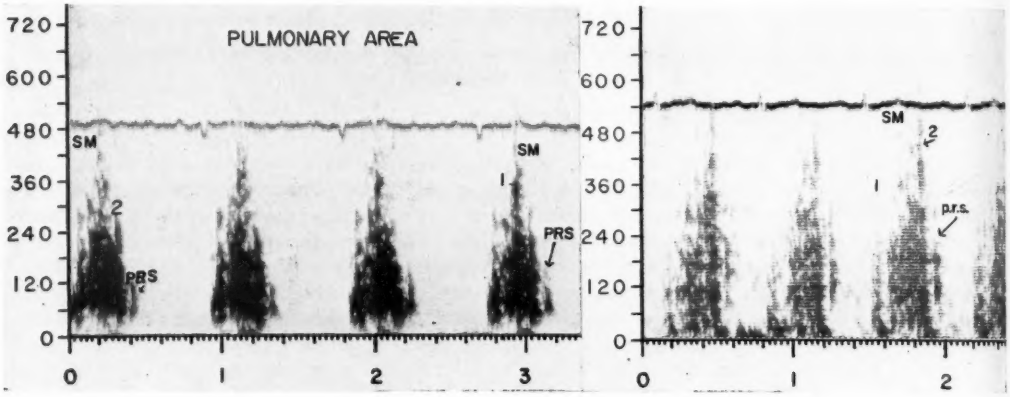


FIG. 1.—(A) Valvular pulmonary stenosis. Demonstrated are (1) the slightly split S_1 with the second component (tricuspid closure) greater; (2) the "Christmas tree" systolic murmur; (3) the unitary second sound; (4) the pulmonary reversal snap.
(B) In this instance the systolic murmur has its peak later in systole. Note the pulmonary reversal snap.

A second feature is the unitary character of the second sound which is loudest in the aortic area and results rather clearly from aortic closure alone.

Thirdly, loudest in the pulmonary area, a diminutive snap-like sound occurs 0·06–0·07 sec. after the aortic closure sound. It appears that this snap is a pulmonary closure sound. Since the pulmonary valve is reduced, in this situation, to a mere membrane with a central perforation, closure in the usual sense is inconceivable. It is more likely that the sound is produced when the membrane, domed into the pulmonary artery during ventricular systole, snaps in the opposite direction with fall in ventricular pressure. The mechanism is analogous to that conceived for the mitral opening snap. Because of the high systolic pressure in the right ventricle and the low pressure in the pulmonary artery the delay in this pulmonary reversal snap (as compared with a normal pulmonary closure sound) is readily understood. Angiocardiographic evidence for the proposed basis of the sound called here "pulmonary reversal snap" has been described to us by Johnson of Stockholm.

By spectral phonocardiography a pulmonary reversal snap of at least faint intensity is demonstrable in most cases of valvular pulmonary stenosis. Because of its low intensity in many cases and the masking effect of the preceding loud systolic murmur the ear is less successful in detecting the sound. Barritt (1954) found a "split second sound" in 11 of 33 cases. Abraham and Wood (1951) described a split pulmonary second sound in 12 of 19 cases of mild stenosis but

in all severe and moderate cases P2 was unitary and of presumed aortic origin. Diagnostically it can be as useful as the opening snap of mitral valve disease. The pulmonary reversal snap disappears after successful valvotomy.

In the fourth place, as was perhaps first indicated by Petit (1902), there may be an early systolic snap which is located shortly after the first heart sound and which may initiate the systolic murmur. This sound presumably results from the abrupt upward doming of the valvular diaphragm.

The low pulmonary diastolic pressure and small size of the orifice in the valvular membrane probably account for the rarity of a pulmonary diastolic murmur in these cases. More puzzling is the reason for the fortunate failure of Brock valvotomy to produce a diastolic murmur in the great majority of cases.

An atrial gallop was demonstrated at the left lower sternal border and/or apex in the majority of cases.

Recently, Vogelpoel and Shrire (1955) have pointed out that the character of the heart sounds permits one to differentiate pulmonary stenosis with intact interventricular septum and interatrial defect (with right-to-left shunt) from tetralogy of Fallot. In the latter condition the systolic murmur usually stops before or just with the aortic closure sound; in the former situation, the systolic murmur tends to extend through the aortic closure sound. Kjellberg *et al.* (1955) reported that in their experience the splitting of the second sound is the same in valvular and infundibular stenosis. However, in the latter type the murmur stopped abruptly with the aortic closure sound, whereas with valvular stenosis the murmur tended to extend beyond this point to the pulmonary closure sound.

Atrial Septal Defect

For purposes of this discussion the auscultatory phenomena associated with this particular type of malformation can be classified in this way.

1. The systolic murmur(s).
2. Systolic click. (a) Early pulmonary systolic click. (b) Mesosystolic click.
3. The diastolic murmurs. (a) Apical rumble. (b) Pulmonary diastolic.
4. Splitting of the heart sounds.
5. Auscultatory features mimicking mitral stenosis.

Basic to a consideration of the systolic murmurs of atrial defect is the mechanism of the left-to-right shunt. Much has been written and speculated on this subject (Brannon *et al.*, 1945; Hickam, 1949; Uhley, 1942; Hall, 1949). Although several of the theories may describe factors contributing to the shunt, it seems most likely—as proposed by Dexter, Dow, and Maloney—that the shunt is *mainly* related to the difference in pressure-volume characteristics of the two ventricles. This is represented schematically in Fig. 2. Pressure-wise the two atria with a large septal defect are essentially one and the two ventricles are filled in diastole from the same head of pressure. The more distensible right ventricle, like the thinner walled balloon of the schema, will accept a larger volume than its thicker walled counterpart. This consideration does not exclude the possibility that some shunt may occur during ventricular systole as a result of the greater distensibility of the right atrium as compared to the left.

From this schema in Fig. 2 it follows that the bulk of the shunt occurs during diastole, not systole. The systolic murmur cannot, therefore, be considered to have its origin at the area of the defect. Satisfactory basis for the systolic murmur is provided by the anatomical state of the outflow tract from the right ventricle and by the increased volume of blood flowing through it. Relative pulmonic stenosis is to be expected from dilatation of the infundibulum below the pulmonary ring and of the pulmonary artery beyond. The existence of such stenosis is supported by demonstration of differences in systolic pressure across the pulmonary valve by catheterization in cases of atrial septal defect.

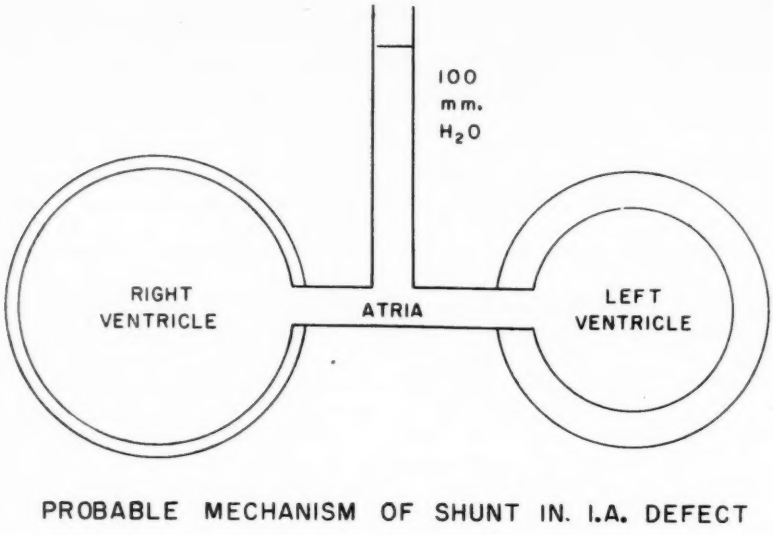


FIG. 2.—The difference in the pressure-volume characteristics of the two ventricles is represented by balloons with different thicknesses of wall. Both are connected to the same pressure head by a T-tube. Obviously the thin-walled balloon dilates more.

The variable intensity of the systolic murmur, including its not infrequent absence, is in keeping with this rather indirect mode of genesis. Systolic murmurs may also result from relative tricuspid insufficiency and, in the case of low atrial septal defects of the ostium primum type with anomaly of the tricuspid and/or mitral valves, from regurgitation at these orifices, especially the latter. The association of a loud apical systolic murmur transmitted well to the axilla with other auscultatory signs consistent with atrial septal defect suggests that the defect is of the ostium primum type as does also the presence of left axis deviation by electrocardiogram.

The early systolic click (Fig. 3 and 4), usually loudest in the pulmonary area, is a frequent finding (Leatham and Vogelpoel, 1954). Dilatation of the pulmonary artery appears to be a *sine qua non* for its presence, but, in our experience, pulmonary hypertension seems to exaggerate this click. A snapping of the artery wall with the onset of ejection seems a plausible explanation.

A mid-systolic click is less commonly heard at the lower left sternal border (Fig. 5). It may be related to right ventricular hypertrophy and dilatation and may actually be produced by movement in costochondral or chondrosternal joints.

Apart from the apical diastolic murmur resulting from associated mitral stenosis, two types of diastolic murmurs are seen: (1) an apical diastolic rumble (Nadas and Alimurung, 1952), and (2) a pulmonary diastolic murmur due to dilatation of the pulmonary ring with or without pulmonary hypertension (Fig. 3 and 4). The apical rumble has been previously demonstrated by spectral phonocardiograph (McKusick *et al.*, 1954 *a*). The possibility that it has its origin at the shunt area must first be considered. Many of the defects have a remnant of fenestrated membrane covering them in part. (See Figs. V-2 and 11–44 by Gould.) The margin of what remains of the interatrial septum might be responsible for such a murmur in other instances. The fact that it is well heard at the cardiac apex is against this view, however, and in general high flow through the tricuspid orifice seems the most likely basis for this murmur.

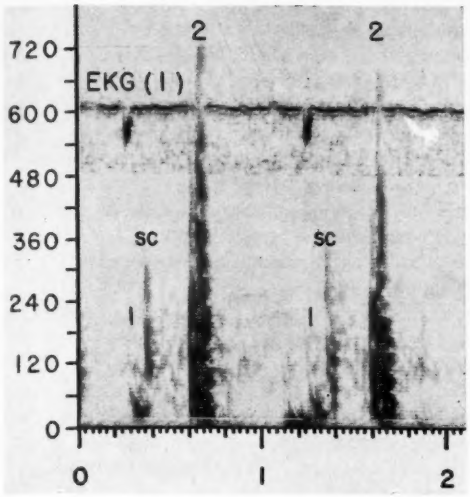


FIG. 3.—Pulmonary area with atrial septal defect. The first heart sound is virtually absent. The conspicuous early systolic click was confused for an unusually snappy S_1. S_2 is split; its second component (pulmonary closure) is greatly accentuated. The early systolic click initiates a soft systolic murmur. A faint early diastolic murmur follows the accentuated pulmonary closure sound.

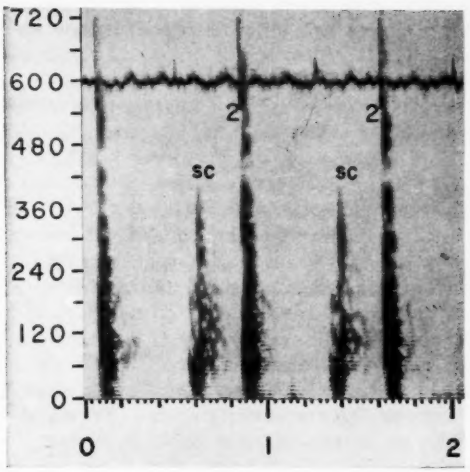


FIG. 4.—Pulmonary area in atrial septal defect. There is a conspicuous early systolic click initiating a faint systolic murmur. An even fainter diastolic murmur follows the accentuated S_2.

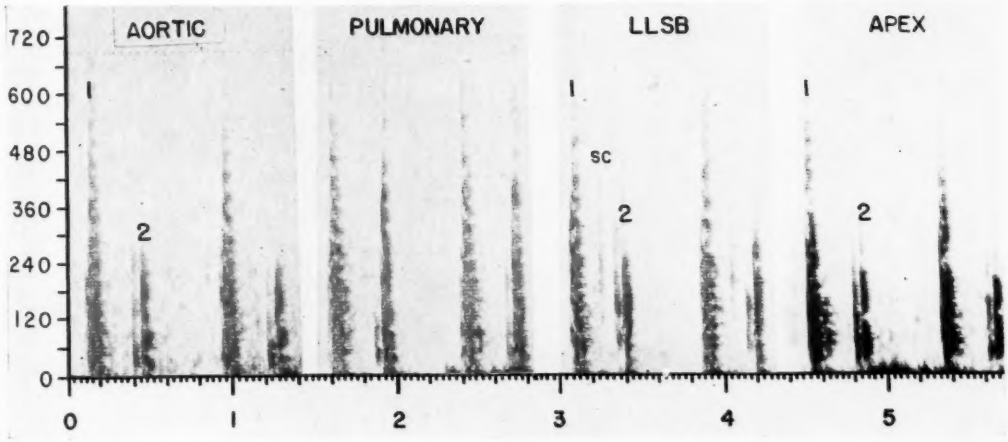


FIG. 5.—Atrial septal defect. Split S_2 with second component (pulmonary closure) accentuated. Mid-systolic click at LLSB.

The experience with other conditions, such as anæmia, mitral regurgitation, ventricular septal defect, patent ductus arteriosus etc. (see below), indicates that when dilatation of the ventricle and increased flow across the mitral orifice co-exist the stage is perfectly set for the development of turbulence and the corresponding rumbling or blubbering diastolic murmur. Both conditions —dilated right ventricle and torrential tricuspid flow—are satisfied in the cases of atrial communication. The audibility of the rumble in the "mitral area" is not surprising in the light of both the dilatation of the right ventricle and the clockwise rotation of the heart as a whole. The quality and timing of the murmur are identical with those of the murmur that results from high mitral flow on bases such as those listed above. Blount *et al.* (1950) described the disappearance of a mid-diastolic murmur at the fourth left interspace after complete surgical closure of the defect.

A pulmonary diastolic murmur occurred in two of eleven thoroughly studied patients. In one the murmur was accentuated during inspiration.

Ventricular asynchronism of pathological degree and resultant splitting of heart sounds occurs principally in two circumstances (Leatham, 1954)—delay of activation of one ventricle as in bundle-branch block, and discrepancy in the stroke volume of one ventricle as compared with the other. Both mechanisms are operative in some cases of atrial defect and the splitting of both heart sounds is exaggerated in these instances. The majority of cases, however, have splitting (Barber *et al.*, 1950) of the second sound (Fig. 3, 5, and 7) which is seemingly related to the great increase in stroke volume of the right ventricle over that of the left. In some cases, even without complete bundle-branch block, splitting of the first sound is also present. Prolongation of isometric contraction in the right ventricle cannot explain such splitting since by definition both the A-V and the arterial valves are closed during this period of the cardiac cycle. However, delay in tricuspid closure as compared with mitral closure is likely to occur in the manner described below, a process which is again related, at least indirectly, to the pressure-volume characteristics of the two ventricles. At the time the ventricles contract with closure of the A-V valves, filling in the case of the left ventricle is likely to be more nearly complete and the mitral leaflets will have floated up toward each other with partial closure. The dilated right ventricle, on the other hand, is likely to be still filling and the tricuspid leaflets to be widely separated. Not only will tricuspid closure be delayed slightly relative to mitral closure but its closure sound will be accentuated since the valves come together from a greater distance. In many ways this delay in tricuspid closure is comparable to

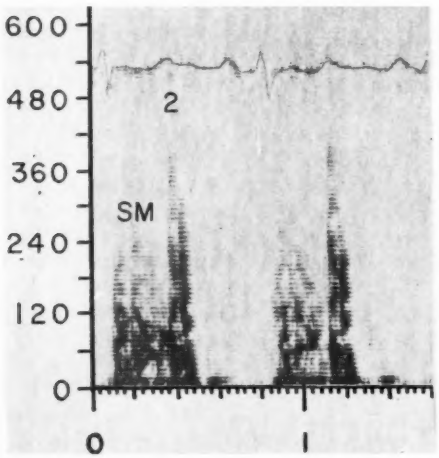


FIG. 6.—Split S_2 at LLSB in atrial septal defect.

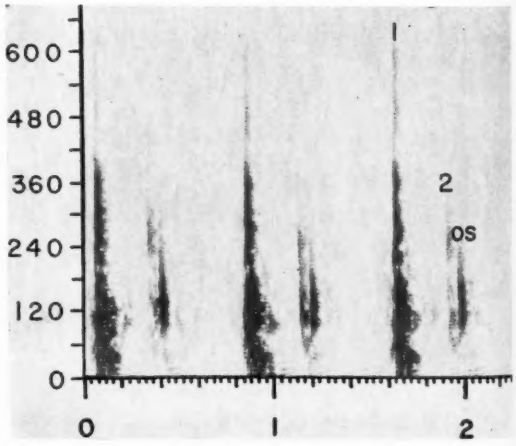


FIG. 7.—For comparison with Fig. 6: S_2 followed by mitral opening snap.

the QRS–S_1 delay, which occurs in atrial fibrillation with shorter diastolic periods as compared to longer ones (Luisada, 1941). Blount *et al.* (1950) illustrated the disappearance of splitting of S_2 after successful complete surgical closure of the defect.

Many of the auscultatory signs of atrial septal defect (as well as the radiological signs) suggest mitral stenosis and lead to that as the primary diagnosis or create an exaggerated impression of the incidence of Lutembacher's syndrome. These mimicking auscultatory signs are

1. the apical mid-diastolic rumble (see above),
2. the pulmonary diastolic murmur suggesting the Graham Steell murmur (Fig. 4),
3. the pulmonary early systolic click,
4. the split second sound which can be mistaken for second sound proper plus mitral opening snap, and
5. a crescendo construction of the first heart sound which simulates a presystolic crescendo and snapping first sound.

In the spectral phonocardiogram and to the experienced ear the mitral opening snap is usually distinguishable from a split second sound. In the case of a split second sound each component has the frequency pattern characteristic of valve sounds (Fig. 6); the opening snap, on the other hand, looks like a snap in the spectrogram (Fig. 7), has more homogeneous frequency content, and usually does not have its frequency " bottom " at the base-line.

Normally mitral valve closure precedes slightly the closure of the tricuspid valve (Leatham, 1954). This temporal separation is often exaggerated in atrial septal defect as is discussed above. Furthermore, the second component produced by tricuspid valve closure is likely to be accentuated. The result (Fig. 8) is a complex easily confused with presystolic crescendo and snapping mitral first sound.

Thoracic Arterio-Venous Fistula

Fistulæ between the aorta or its intrathoracic branches and the vena caval system or pulmonary artery produce murmurs that are continuous as a rule and have a characteristic time-frequency-intensity pattern. Murmurs that show this pattern are those of patent ductus arteriosus, the artificial ductus of the Blalock-Taussig anastomosis, aortic septal defect, intercostal or coronary

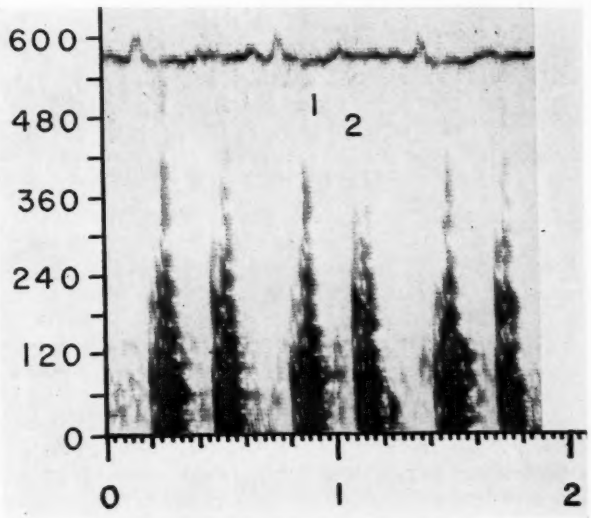


Fig. 8.—Crescendo construction of S_1 with atrial septal defect.

A-V fistulæ, and even thyroid bruits. Pulmonary A-V fistulæ probably show the same pattern. Venous hums are likewise usually indistinguishable. The principal practical usefulness is the opportunity the pattern provides for distinguishing this type of lesion from stenosis and regurgitation of the aortic or pulmonary valve. This application is well illustrated by the case represented in Fig. 13.

Fig. 9 presents the typical pattern and the features distinguishing it from that of stenosis-regurgitation at an arterial orifice. The continuous murmur of thoracic A-V fistula has a peak of intensity and frequency span in the vicinity of the second heart sound. On the other hand, in aortic stenosis and regurgitation, for example, two peaks of intensity and frequency are generally present. The ejection stenosis murmur in systole has a " Christmas tree " configuration as a result of the peak of frequency and intensity in mid-systole. The diastolic murmur has a peak at or soon after the second sound with diminuendo thereafter. In Fig. 10 is presented the typical auscultatory finding in patent ductus arteriosus.

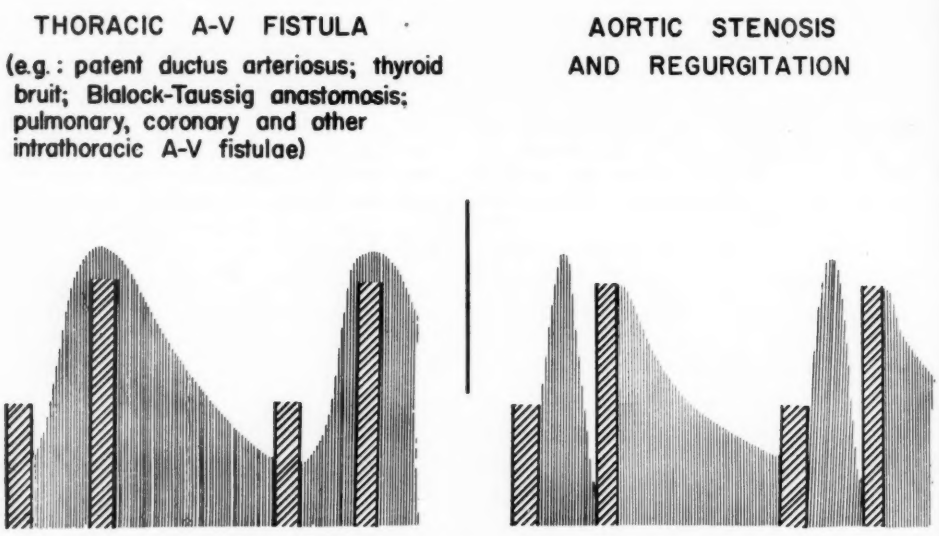

THORACIC A-V FISTULA
(e.g.: patent ductus arteriosus; thyroid bruit; Blalock-Taussig anastomosis; pulmonary, coronary and other intrathoracic A-V fistulae)
AORTIC STENOSIS AND REGURGITATION

FIG. 9.—Comparison of the frequency-time pattern of the murmur of thoracic arterio-venous fistula with that of aortic stenosis and regurgitation.

As in other congenital anomalies with which a dilated pulmonary artery is associated, an early pulmonary systolic click may occur with patent ductus arteriosus. The spectral phonocardiogram of such a case has been shown elsewhere (McKusick *et al.*, 1954 *b*). Occasionally there is a pulmonary systolic murmur, produced in the dilated pulmonary artery, distinct from the systolic component of the continuous murmur. In such instances the pulmonary systolic murmur is likely to be introduced by the early systolic click. The recording in Fig. 12 is from a patient with patent ductus and pulmonary hypertension. There was no continuous murmur. In the recording from the pulmonary area there is diminuendo systolic murmur initiated by an early systolic click.

At the apex a low-pitched rumbling mid-diastolic murmur is occasionally heard with patent ductus arteriosus (Ravin and Darley, 1950). It appears to be the murmur of relative mitral stenosis resulting from two factors—torrential mitral flow and dilatation of the left ventricle. Fig. 11 presents an example in a patient with typical auscultatory and operative findings of patent ductus: in this instance the sound is circumscribed, rather suggesting a summation gallop, but it begins too late to be a third-sound gallop and too early for atrial gallop.

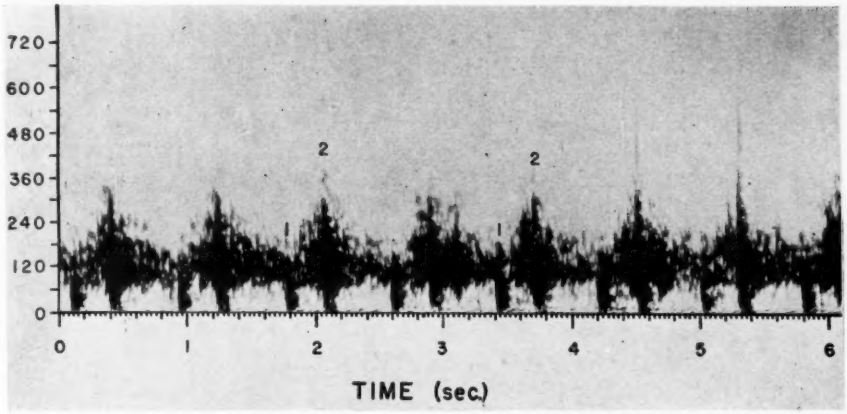


FIG. 10.—Typical murmur of patent ductus arteriosus.

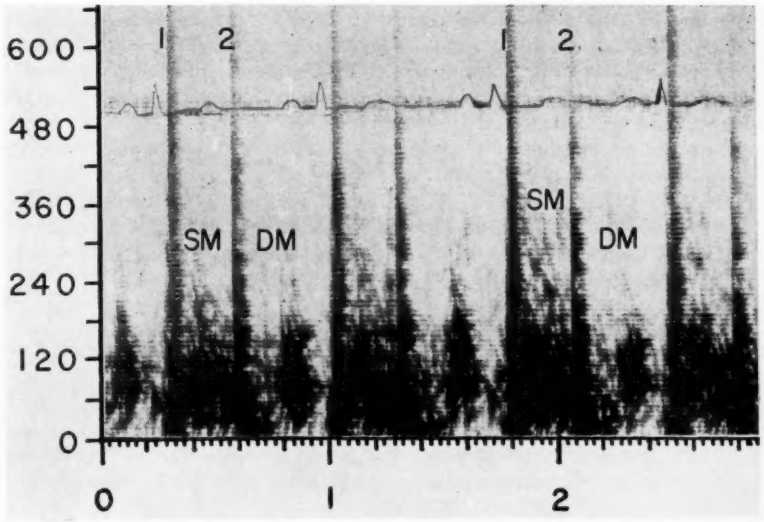


FIG. 11.—Mid-diastolic rumble at apex in patent ductus.

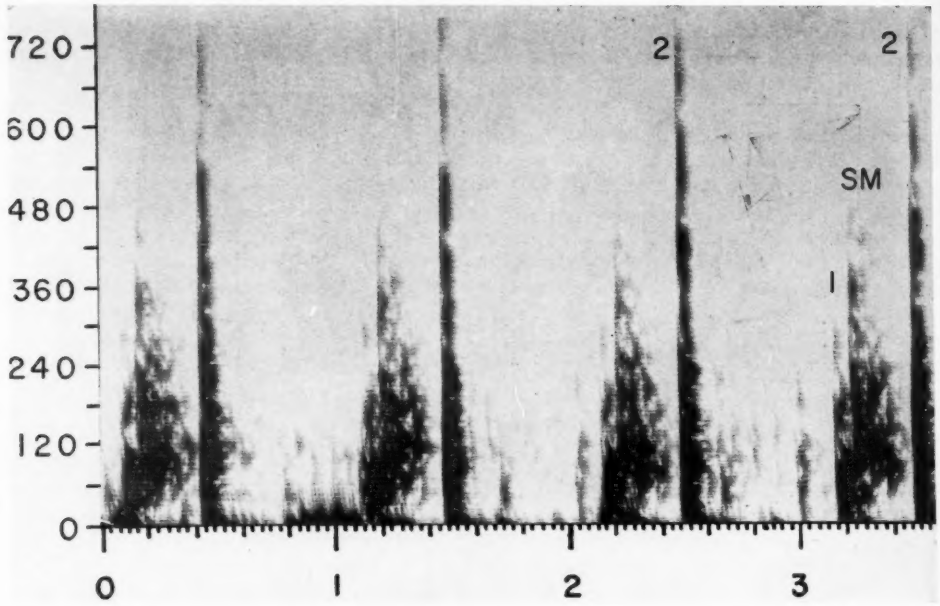


FIG. 12.—Patent ductus arteriosus with pulmonary hypertension (pulmonary area). An early systolic click initiates a diminuendo systolic murmur. P_2 is greatly accentuated.

In Fig. 13 is presented the sound recording in the third right interspace of a patient in whom this type of study was diagnostically helpful. This 50-year-old coloured woman has been followed at this hospital for 17 years. The murmur and cardiac enlargement have been present throughout but both have apparently increased slowly over the years. The patient has had virtually no symptoms referable to the heart and her pulse pressure has been normal. However, her diagnosis has been aortic stenosis and regurgitation throughout. With the passage of years right axis deviation has developed in the electrocardiogram (which previously showed normal axis) and in recent months atrial fibrillation has set in. These developments are not surprising in the light of the pronounced enlargement of the right atrium and right ventricle on angiocardiograms. The enlargement of the right side of the heart appears to be mainly a matter of dilatation with little hypertrophy. On auscultation a continuous murmur loudest in the third right interspace was heard. By stethoscope the murmur seemed to " peak " in the vicinity of the second heart sound. This impression was confirmed by the spectral phonocardiogram (Fig. 13).

Further studies in this patient have been impossible. However, the evidence of left-to-right shunt of the intrathoracic fistula type is very strong.

Bonham-Carter and Walker (1955) have recently indicated two other bases for a continuous murmur that may be difficult to distinguish from that of patent ductus arteriosus: (1) ventricular septal defect with pulmonary regurgitation; and (2) large tortuous collateral vessels as with truncus arteriosus or pulmonary atresia.

PRIMARY PULMONARY HYPERTENSION

The principal auscultatory features of two illustrative cases, one adult and one juvenile, will be demonstrated. In both the disease is thought to be of congenital origin.

The first patient, 6 years old, whose heart sounds are illustrated in Fig. 14 had a pulmonary

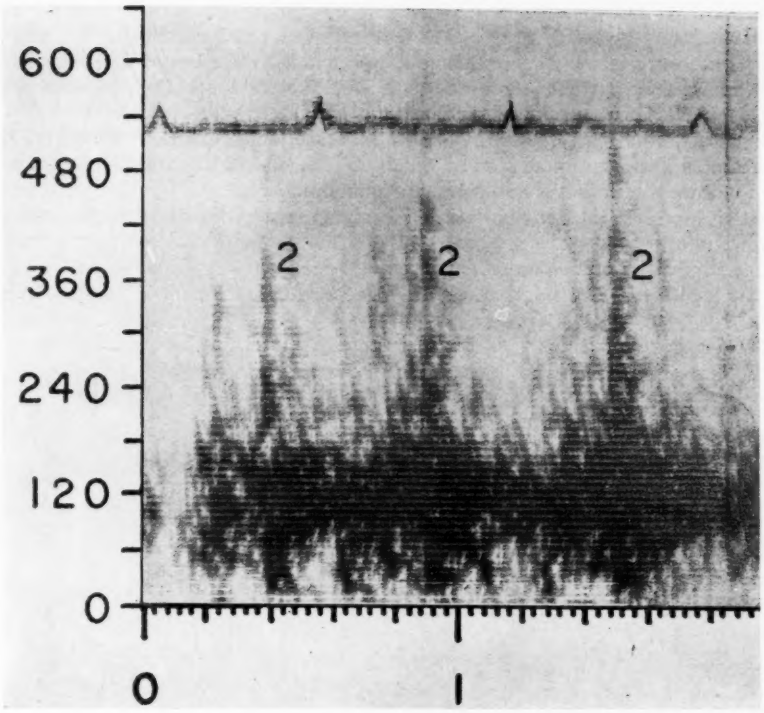
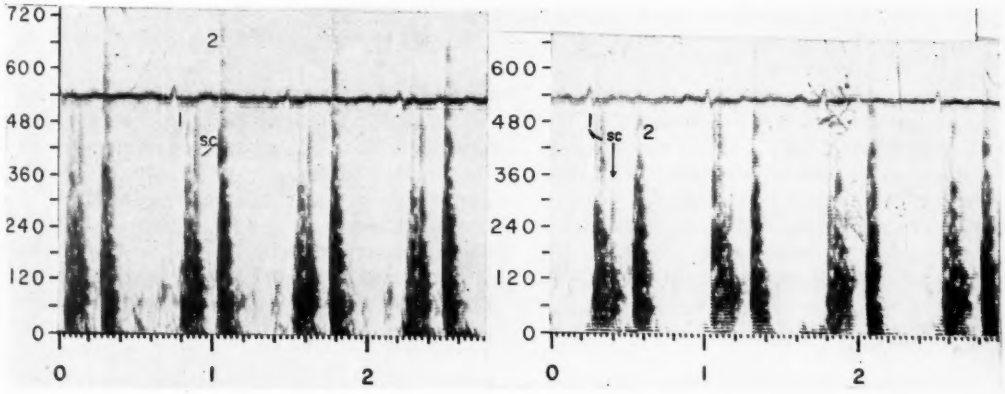


FIG. 13.—Thoracic arteriovenous fistula, congenital.



A B

FIG. 14.—Primary pulmonary hypertension. S_2 is greatly accentuated. S_1 is split at apex (B). An early systolic click is loudest in the pulmonary area (A).

arterial pressure of 97/73 with a mean of 85 mm. Hg by cardiac catheterization and a much dilated main pulmonary artery by radiography. The features of note are as follows.

1. The second sound is greatly accentuated in both intensity and frequency span. It is not split. It is worthwhile reiterating that, contrary to the common misconception, hypertension of either arterial circuit, is not *per se* a cause of significant or consistent splitting of S_2.

2. An unusually loud early systolic click (" SC ") in the pulmonary area (Fig. 14A) understandably created a mistaken impression of widely split S_1 on auscultation. It seems to be mainly the tricuspid closure sound that is audible in the pulmonary area.

3. That the sound labelled as early systolic click is indeed so is strongly indicated by the relatively long time interval between it and QRS. The matter is clinched by examination of the recording at the apex (Fig. 14B) where three sounds are demonstrated. These can, with considerable confidence, be identified successively as mitral closure sound, tricuspid closure sound, and early systolic click.

4. An atrial gallop is present. A faint third heart sound was demonstrated in some cycles.

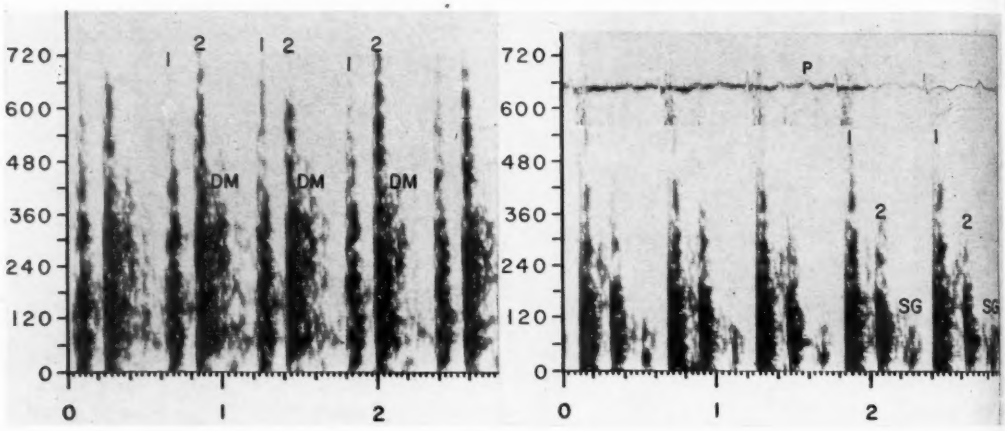


FIG. 15.—Primary pulmonary hypertension. In the pulmonary area (A) the greatly intensified pulmonary closure sound seems to continue directly into a loud diastolic murmur. A summation gallop is demonstrated at the apex (B).

The second patient, whose recordings are displayed in Fig. 15, is 29 years old. The pressure in the main pulmonary artery was 134/67 with a mean of 89 mm. Hg. At the pulmonary area (Fig. 15A) the second sound is tremendously accentuated in both intensity and in frequency span and continues directly into a diastolic murmur of the Graham-Steell type. At the apex (Fig. 15B) the first heart sound is slightly split. The second component of the split first sound, undoubtedly produced by tricuspid closure, is greatly accentuated. There is a systolic murmur. In mid-diastole there is a summation gallop. On auscultation this seemed to be a mid-diastolic rumble. However, the P–R interval was 0·26 seconds and close inspection reveals that when a longer murmur-like sound is present, two sounds, third heart sound and atrial sound, can be identified as contributing to it.

CONGENITAL MITRAL STENOSIS

Recordings were made from a one-year-old infant with classical auscultatory, radiographic (including angiocardiographic), operative, and necropsy findings of mitral stenosis. The pathological features supported the clinical opinion that the mitral valve disease was of congenital rather than rheumatic origin.

The spectral phonocardiogram in this case is identical with that seen in most cases of rheumatic mitral stenosis in adults (McKusick *et al.*, 1954 *b*; 1955). The features of note, as illustrated in Fig. 16, are as follows.

1. The mitral closure sound (1) is snapping (as indicated by the conspicuous harmonics, e.g. the one at about 420 c.p.s.), is intensified and is delayed in relation to the QRS.

2. There is a diminuendo systolic murmur denoting a certain degree of concomitant mitral regurgitation.

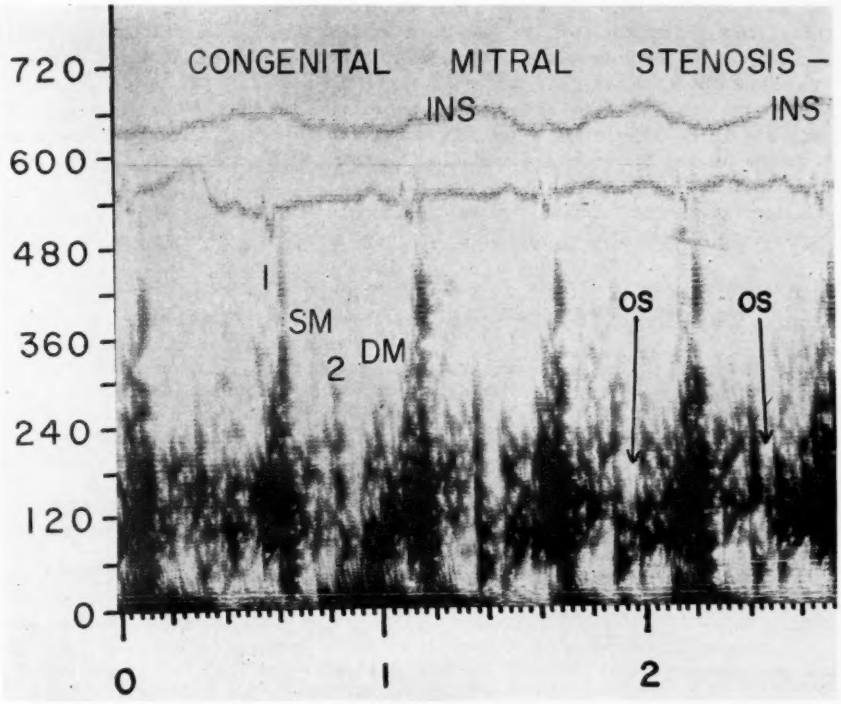


FIG. 16.—Congenital mitral stenosis. Apex. Inspiration (INS), opening snap (OS), the first and second heart sounds (1 and 2), the systolic murmur (SM), and the diastolic murmur (DM) are marked.

3. There is a suspicion of a diminutive opening snap (OS) following the second heart sound. The impression of opening snap was strengthened by examination of the recordings from the pulmonary and left lower sternal areas. These revealed, in addition to identifiable aortic and pulmonary closure sound, a sound that was located at the same point in the cardiac cycle as the presumed opening snap at the apex, which was appreciably louder at these sites and had the spectrographic characteristics previously described for snaps in general and the mitral opening snap in particular.

4. The diastolic rumble is initiated by a circumscribed sound with the temporal characteristics of a third heart sound.

5. The diastolic rumble is first diminuendo in both intensity and peak frequency.

6. Following the P wave of the electrocardiogram and building up to the snapping mitral

closure sound, the diastolic rumble becomes greatly accentuated with a crescendo in respect both to intensity and to peak frequency.

Except for the additional feature of a systolic murmur, Duroziez's onomatopœic device, " fout-ta-ta-rou," is rather accurately reproduced.

Necropsy revealed that the mitral valve was diaphragmatic with a small central perforation.

Summary and Conclusions

The spectral phonocardiographic patterns in thoracic A-V fistula (exemplified by patent ductus arteriosus), in pulmonary stenosis, and in atrial septal defect are sufficiently distinctive to suggest the diagnosis from examination of the sound recordings alone. The pulmonary reversal snap of valvular pulmonary stenosis is highly diagnostic, particularly when combined with a murmur of the typical ejection stenosis type.

Although most reported cases of congenital mitral stenosis have not had completely typical auscultatory findings in terms of the experience with rheumatic mitral stenosis, a case is presented in which typical auscultatory findings, including a mitral opening snap, did occur. Such cases might be particularly favourable for valvotomy.

Some features of the heart sounds in primary pulmonary hypertension have been demonstrated. Exaggerated splitting of the second pulmonary sound is not a feature.

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CASE REPORTS

PATENT DUCTUS ARTERIOSUS WITH PROGRESSIVE DILATATION OF THE PULMONARY ARTERY

BY

J. A. COSH

From the Department of Medicine, University of Bristol

A patient with patent ductus arteriosus was observed over a period of years to have progressive increase in size of the pulmonary artery. This was accompanied by the development of a pulmonary diastolic murmur and thrill, and of electrocardiographic changes of right ventricular hypertrophy with bundle-branch block. She died, aged 39 years, of pulmonary embolism.

Case History

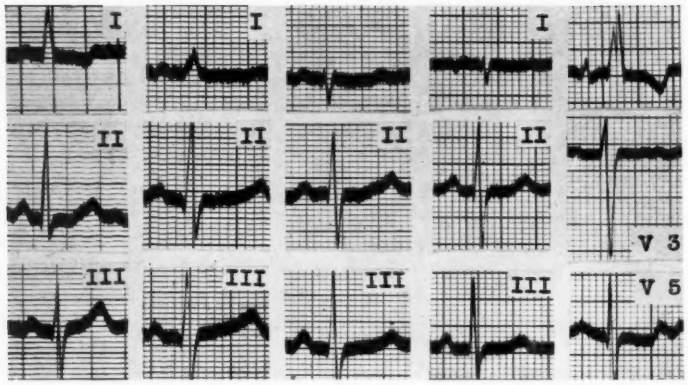
The patient was born in 1913. A heart murmur was noticed in childhood, but she apparently led a normally active life and had no symptoms as a child.

At age 23 she had pneumonia, and after recovery became aware for the first time of dyspnœa on effort. A year later she was admitted to the Bristol General Hospital under Professor C. B. Perry as a possible case of bacterial endocarditis. No proof of this was found. She was then of average physique and normal colour, with no finger clubbing and no venous congestion or œdema. The apex beat was in the fifth left intercostal space beyond the mid-clavicular line, and the impulse was forceful in character. A systolic thrill was felt at the pulmonary area, where there was a continuous murmur. B.P. 140/?40. A diagnosis of uninfected patent ductus arteriosus was made. The electrocardiogram (Fig. 1) showed evidence of left ventricular hypertrophy. In the following year she bore a child without difficulty; the child's heart was normal.

When the patient was re-examined at the age of 28 years the only change noted was that a diastolic murmur was now heard to the left of the sternum. X-ray showed enlargement of the heart and great prominence of the pulmonary artery, which was seen to pulsate vigorously on fluoroscopy. Two years later a second pregnancy was terminated at the fourth month by hysterotomy. In the next three years her condition remained unchanged. Her weight was 102 lb. and height 62 inches. The X-ray appearances at age 32 are shown in Fig. 2.

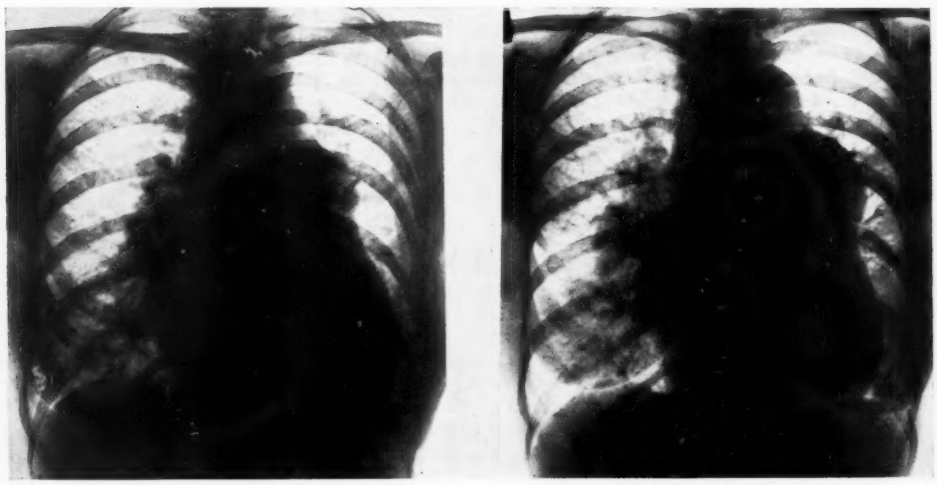
The diastolic murmur to the left of the sternum was noted to be louder, and accompanied by a thrill, when the patient was seen again at the age of 35. X-ray showed the main pulmonary artery to be larger than it was three years previously. B.P. 140/60. The electrocardiogram now showed right axis deviation (Fig. 1).

In 1952, when she was 39 years of age, the patient attended hospital for the last time. Dyspnœa on effort and fatigue towards evening were troublesome but not incapacitating. Her colour was normal, with no cyanosis or finger clubbing, and there were no signs of congestive failure. The apex beat was in the fifth interspace, 2·5 cm. beyond the mid-clavicular line, and the impulse was abrupt and forcible. A coarse diastolic thrill was felt to the left of the sternum, most obviously in the third left interspace. The first sound was loud at the apex, and the second sound loud at the pulmonary area. The continuous murmur was still present at the pulmonary area, and the diastolic murmur to the left of the sternum was rasping. The blood pressure was 140/70. X-ray and fluoroscopy showed that the heart was considerably enlarged; the aorta and main pulmonary artery were dilated and exhibited vigorous pulsation, which was also obvious in the chief branches of the pulmonary arteries. The main pulmonary artery was even more prominent than before (Fig. 2). The electrocardiogram showed right bundle-branch block and right ventricular hypertrophy (Fig. 1).



Age 24 32 35 39 years

FIG. 1.—Electrocardiograms showing change from left ventricular hypertrophy at age 24 to right bundle-branch block and right ventricular hypertrophy at age 39. The unmarked lead in the upper right corner is V1.



A B

FIG. 2.—Teleradiograms showing the increase in prominence in the main pulmonary artery and aorta between the ages of 32 years (A) and 39 years (B). There is little accompanying change in the heart size or the heaviness of the pulmonary vascular shadows.

Three months later the patient was found dead in bed at home, having apparently been in her usual health the night before.

Necropsy Findings

Examination was limited to the thorax and abdominal cavity. The external appearances were normal.

Heart. Pericardium normal, no effusion. Heart weight 570 g. There was well-marked hypertrophy of the right (1·1 cm.) and left (2·0 cm.) ventricular walls, and both chambers were dilated. A well-defined

area of endocardial thickening was seen below the cusps of the pulmonary valve (Fig. 3). There was a little generalized thickening of the endocardium of the left atrium, and the cusps of the mitral, aortic and pulmonary valves were a little thickened, but with no naked-eye evidence of rheumatism. The auricles contained no clot. The circumference of the aorta was 6·3 cm. at 3 cm. above the valve, and 7 cm. at the valve orifice (normal 7·7 to 8·0 cm.). There was a localized dilatation of the aorta at the site of the *patent ductus*. The ductus orifice measured 0·8 × 0·5 cm.; the aorta and pulmonary artery were in close contact

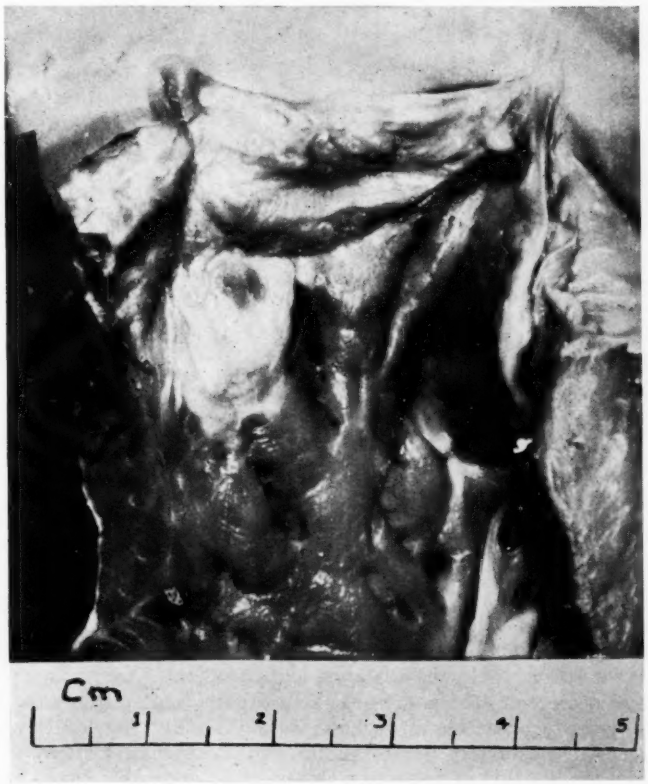


FIG. 3.—Pulmonary valve cusp and the thickened patch of endocardium immediately below, caused by regurgitation.

at this point, and the ductus had no appreciable length. The main pulmonary artery was much dilated, and its circumference at the valve was 10·3 cm. compared with the normal 8·5 to 9·0 cm. (Ross, 1948). There was no endocardial thickening either on the aortic or pulmonary arterial walls opposite the opening of the ductus. The right pulmonary artery was blocked by a large embolus, the origin of which was not found. The larger branches of the pulmonary artery were dilated, and their walls thickened, showing small scattered patches of atheroma.

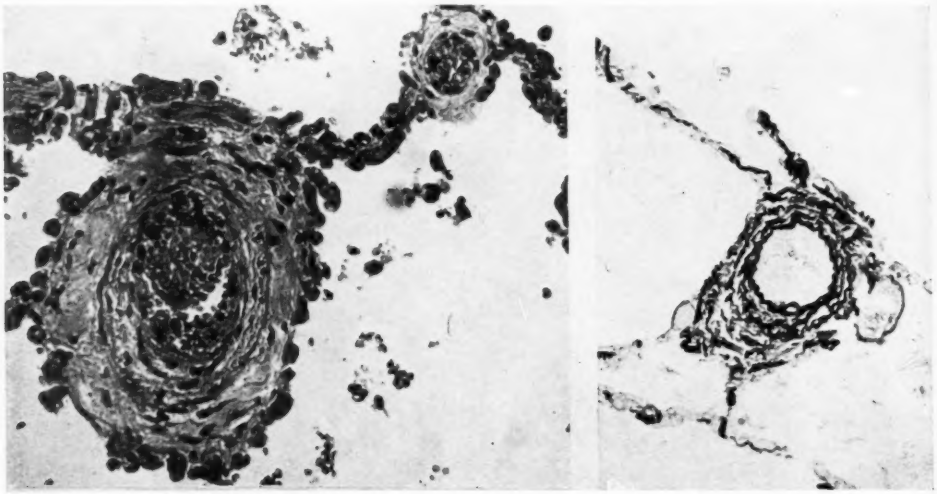
Lungs. Pleural cavities normal. There was some brown induration at the bases of the lungs, but no other abnormality.

Abdomen. The spleen was nearly twice the normal size, and other organs were normal.

Histology. Left auricle: hypertrophy and endocardial fibrosis. The mitral valve showed irregular

fibrous thickening. The cusps of the pulmonary valve were covered with a thin layer of organizing fibrin and irregularly scarred. The left and right ventricles were hypertrophied, with no evidence of rheumatism.

In the lungs there were well-marked changes of pulmonary hypertension; the small arteries showed medial hypertrophy and fibro-elastic intimal thickening (Fig. 4).



A B

FIG. 4.—Histology of the small arteries of the lung, showing (A) medial hypertrophy and intimal thickening, (B) increase in the elastic fibres in the intima and media.

Interpretation

The finding of a characteristic Gibson murmur on every examination between the ages of 23 and 39 years is evidence that the shunt was in the usual direction, i.e. from the aorta into the pulmonary artery. It appears to have been a large shunt in view of the wide systemic pulse pressure, the hypertrophy of the left ventricle, the dilatation and pulsation of the pulmonary artery, and the size of the ductus at necropsy. The patch of endocardial thickening below the pulmonary valve cusps is evidence of gross regurgitation through the valve. The histology of the pulmonary arteries indicates the presence of pulmonary hypertension; right ventricular hypertrophy would well be accounted for by the combination of pulmonary hypertension and pulmonary regurgitation.

The unusual features of this case are the development of pulmonary regurgitation, becoming more obvious as the pulmonary artery increased in size, and the electrocardiographic change from the pattern of left ventricular hypertrophy to that of right ventricular hypertrophy with right bundle-branch block.

Discussion

The association of pulmonary hypertension with patent ductus is well known (Cosh, 1953; Dammann *et al.*, 1953; Lukas *et al.*, 1954; Whitaker *et al.*, 1955). In the most severe type the pulmonary vascular resistance is so great that the pulmonary arterial pressure may roughly equal the aortic, so that a continuous murmur is not heard. In the mildest type the pulmonary resistance is of normal degree, and the pressure is raised merely passively by the presence of an increased pulmonary blood flow. This patient appears to occupy an intermediate position between these types. The histology of the pulmonary vessels suggests a considerable increase in resistance, so

that, in the presence of a large left-to-right shunt the pulmonary arterial pressure would be high; yet the presence of a continuous murmur indicates that the pulmonary arterial pressure remained lower than the aortic.

It is not known whether the pulmonary arterial pressure remained at the same level over the last decade of life, or whether it progressively increased, as appears to have happened in a similar case described by Harris (1955). Although the electrocardiographic changes suggest the latter, they may only reflect the development of pulmonary regurgitation and the resulting increased strain on the right ventricle. Presumably after many years the pulmonary artery became sufficiently dilated to give rise to valvular incompetence. The resulting big pulse pressure in the pulmonary artery may have been a factor in aggravating the dilatation and incompetence.

Dilatation of the pulmonary artery is a common finding in patients with patent ductus arteriosus. Progressive dilatation is unusual, and was not found in a review of 73 cases, many of whom were followed into adult life (Cosh, 1956). One of the cases of patent ductus reviewed by Campbell (1955, Case 19) had an increase in the size of the heart and main pulmonary artery over the course of ten years, when pulmonary hypertension had caused reversal of the flow through the ductus; she died after ligation of the ductus. Great dilatation, with rupture of the pulmonary artery into the pericardium, has been reported by Durno and Langdon Brown (1908) and by Moench (1924). Saccular aneurysms of the pulmonary artery accompanying patent ductus have been described by d'Aunoy and von Haam (1934).

Operative closure of the ductus in this patient would clearly have been hazardous, although it might well have been easier earlier in life before such great dilatation of the pulmonary artery occurred.

I wish to thank Professor C. Bruce Perry for permission to report this case, and Dr. O. C. Lloyd, Lecturer in Pathology, University of Bristol, for his report of the necropsy.

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CARDIAC FAILURE DUE TO PRIMARY AMYLOIDOSIS

BY

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Primary amyloidosis is considered to be a rare disease. In 1939 Lindsay and Knorp reviewed 49 cases, and since then approximately 30 more have been recorded. The condition is important in the differential diagnosis of congestive cardiac failure of obscure origin. It may present a difficult clinical problem, as in the case reported here.

Case Report

In September, 1953, a woman of 46 years, who had previously been well, developed swelling of the ankles. This gradually increased until in February, 1954, she was admitted to hospital. She was treated in bed with a low sodium diet and mersalyl, and in March she was discharged home, free from œdema. Two months later the symptoms returned and she was readmitted. The congestive failure again responded to rest and mersalyl. She was transferred to the Middlesex Hospital in August with a diagnosis of either constrictive pericarditis or myocarditis with failure.

She was a pale, well-covered woman with a slightly hoarse voice. Pulse regular, 96 a minute. Blood pressure, 110/80. Venous pulsation was visible one inch above the sternal angle at 45°, and the liver was enlarged three finger breadths below the costal margin. There was ascites and gross œdema of sacrum and legs. There were no palpable cardiac pulsations. The heart sounds were faint. There was an apical presystolic gallop but no murmurs were heard. The lungs were dry and the spleen was impalpable.

Urine: heavy albuminuria; total urinary protein 10·9 g. in 24 hr.; deposit: some leucocytes, epithelial cells, and hyaline casts in some specimens. Electrocardiogram showed sinus rhythm and low voltage QRS complexes with flat T waves. Chest X-ray: increased transverse diameter of heart; lung fields clear; no pericardial calcification. Radioscopy: diminished cardiac pulsation. Blood count and hæmoglobin normal. E.S.R., 39 mm. in one hour. W.R. negative.

Blood urea normal. Urea clearance, renal function 49 per cent. Serum cholesterol, 560 mg. per 100 ml. Serum proteins, total, 4·7 g. per 100 ml. (albumin 2·1; globulin 2·6). Electrophoretic pattern of serum proteins showed grossly increased alpha 2 band. No amyloid seen in gum biopsy, and no " L.E." cells in blood smear. B.M.R., plus 1 per cent.

Cardiac catheterization and angiocardiography were unsuccessful because of a venous anomaly which prevented the catheter from being passed beyond the neck.

In spite of treatment in bed with a low sodium high protein diet, mercurial diuretics, and katonium, the œdema increased rapidly and heavy albuminuria continued. Acupuncture was performed and 17 pints of œdema fluid were drained from the legs in 24 hours. Drainage was then discontinued as the patient became drowsy and complained of nausea. The serum electrolytes at that time were within normal limits. The venous pressure remained raised and she continued to retain fluid. The blood urea rose from normal to 79 mg. per 100 ml. On November 16, auricular fibrillation commenced and the blood pressure dropped to 90/60 mm. Hg. Suddenly death took place on November 26.

Necropsy. There was congestive cardiac failure with 5 pints of ascitic fluid, systemic œdema, and a nutmeg liver. No evidence of pericardial fibrosis was found, but there was generalized hypertrophy of the myocardium which contained a number of greyish waxy plaques. The lungs, kidneys, and spleen appeared normal. There was no evidence of chronic suppuration or tuberculosis.

Histology. The myocardium was infiltrated by an amyloid-like substance, deposited in the walls of capillaries and arterioles and around the myocardial fibres. Deposits of a similar material were present in the walls of capillaries, arterioles, and small arteries throughout the body, particularly those of the liver, spleen, suprarenals, and tongue. There was heavy infiltration of the basement membrane of sweat glands

and some of the thyroid acini. The same substance was present in the basement membrane of the renal glomerular tufts and in the walls of the afferent arterioles. Some renal tubules showed hyaline degenerative changes.

The infiltrating material had the morphological appearance of amyloid, but failed to take up the usual dyes. It stained normally with hæmotoxylin and eosin but did not stain metachromatically with methyl violet. There was no affinity for iodine and only a slight affinity for Congo red. No reaction was seen with the per-iodic acid Schiff technique, as would have been expected in a collagen disease. In view of its typical appearance with hæmotoxylin and eosin and its distribution, there was little doubt that this was either amyloid or a very closely related substance.

Discussion

Primary systemic amyloidosis was first described by Lubarsch (1929), who formulated the following criteria for the condition: (1) the absence of a predisposing factor such as chronic suppuration, (2) the failure of the amyloid deposit to show the usual staining reactions, (3) the absence of involvement of organs commonly affected by secondary amyloid, and (4) extensive deposits in the heart, blood vessels, skin, and skeletal muscle.

The present case fulfils the first and second criteria. Concerning the third and fourth criteria, the common sites of secondary amyloidosis include the parenchymatous organs such as the spleen, kidney, liver, and adrenals. In primary amyloidosis, however, these organs tend to be spared, while the cardiovascular system, muscle, skin, lungs, and gastrointestinal tract are extensively involved. In the present case, the parenchymatous organs as well as the cardiovascular system and skin were involved, thus combining some of the features of both primary and secondary amyloidosis. A similar case was recorded by Hartney *et al.* (1949).

The electrophoretic pattern of the serum proteins was of particular interest, as it showed a greatly increased alpha 2 band, a pattern typical of the nephrotic syndrome. This abnormality, combined with the heavy proteinuria and the high serum cholesterol (560 mg. per 100 ml.), suggested that considerable amyloid deposits would be found in the kidneys. Microscopy confirmed generalized renal infiltration of moderate degree. An increase in the alpha 2 fraction may also occur in congestive cardiac failure and in constrictive pericarditis (Hardwicke, 1954), and the cardiac failure may have contributed to the electrophoretic pattern in the present case. In regard to the raised serum cholesterol, it may be significant that the thyroid gland was also involved. Again, the heavy amyloidosis of the liver may have been a factor in the serum cholesterol level, and could account for the altered albumin : globulin ratio (2·1 : 2·6).

In primary amyloidosis a presenting picture of congestive cardiac failure due to myocardial involvement is not uncommon. Dahlin (1949) states that death from cardiac causes occurs in over half these cases. This condition should therefore be considered in cases of congestive failure which prove refractory to the standard treatment or in which the underlying ætiology is obscure. Constrictive pericarditis or pericardial effusion may enter into the differential diagnosis, as in the present case, in which a raised venous pressure and generalized œdema were combined with a quiet impalpable heart. The question of operative treatment then arises. The presence of pericardial calcification on radioscopy will confirm the diagnosis of constrictive pericarditis. In equivocal cases, cardiac catheterization or angiocardiography may be necessary. A characteristic pulse form in the right ventricle and right atrium is obtained in constrictive pericarditis (McKusick, 1952). Injection of contrast medium through the catheter in the right atrium will demonstrate a thickened pericardium or a pericardial effusion (Wood, 1951). In the present case, neither of these tests could be performed, and the diagnosis was in doubt until necropsy.

A positive diagnosis of primary amyloidosis may sometimes be made by means of the Congo red test (Bennhold, 1923; Wade, 1954) or by the recovery of amyloid tissue from gum, skin, or muscle biopsy. Negative results, however, do not exclude the diagnosis, as shown by the gum biopsy in the present case.

Summary

A fatal case of primary systemic amyloidosis is recorded, in which myocardial involvement caused congestive cardiac failure.

I wish to thank Dr. R. Howard who referred the case to hospital, Dr. W. Somerville under whose care the patient was admitted to the Middlesex Hospital, and Dr. P. Andrews for the post-mortem examination.

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HEART FAILURE DUE TO EXTREME OBESITY

BY

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Diseases that restrict the respiratory excursions of the chest for a long period may lead to cor pulmonale but obesity is not usually recognized among them. The following report is of a case of cor pulmonale from extreme obesity.

Case Report

A woman, aged 40, was admitted to hospital with the complaints of obesity and recent dyspnœa and cyanosis. She had been moderately obese in childhood, and weighed 11 st. 3 lb. (71 kg.) in 1935 and 13 st. 2 lb. (83 kg.) in 1939. Thereafter her weight increased grossly and in 1951 she weighed about 20 st. (127 kg.). A low calorie diet and dextro-amphetamine temporarily halted the increase, but she began again to put on still more weight. Otherwise, she had always enjoyed good health and remained well until six months before admission.

At that time, she had had a severe cough, without sputum, for about three weeks. Afterwards, she became still stouter and noticed a hard thickening of the substance of the anterior abdominal wall which later spread up over the front of the chest. Her sister noticed that when the patient laughed her face became blue. She developed increasing dyspnœa, especially on effort; shortly before admission she could just manage one flight of stairs.

On admission her weight was approximately 26 stones (364 lb. or 165 kg.) (height 5 ft. 8 in.). Her girth was enormous. She was encased in masses of fatty tissue which over the torso had a hard unyielding quality. There was elephantiasis of the mons veneris and labia. By comparison with the torso the limbs were slender, though themselves very adipose. There was peau d'orange on the lower abdomen and on the pendulous breasts. The skin nowhere pitted very much and then only after prolonged, firm pressure and its appearance and texture resembled those of lymphœdema, especially on the trunk.

Her face was suffused and there was moderate cyanosis. She was not dyspnœic at rest, but the effort of moving herself about in bed made her very breathless. The jugular venous pressure could not be truly assessed but was probably grossly raised. There was gross papillœdema with enormously distended retinal veins and numerous retinal hæmorrhages chiefly distributed in relation to the veins. The ocular fundi were most reminiscent of the appearances seen sometimes in advanced emphysema heart failure.

No abnormality could be detected on examination of the heart and lungs themselves. The blood pressure was 130/90. The electrocardiogram showed general low voltage. The oxygen saturation of the blood (by ear oximetry) was 57 per cent, increasing to 79 per cent on inhalation of oxygen. The hæmoglobin was 15·2 g. No vital capacity greater than the tidal air could be recorded.

Oxygen inhalations, digitalis and a mersalyl injection did little to benefit her condition and she died suddenly five days after admission.

Post-mortem Examination. Although the body had been in the refrigerator the internal organs were still warm owing to the insulating power of the adipose tissues and a certain amount of autolysis had taken place. The peritoneal sac contained a litre of ascitic fluid. The heart weighed 640 g. There was slight atheroma of the right coronary artery but all the coronary vessels were patent. The heart valves were normal. The right ventricle was 7 mm. thick in its outflow pathway and the left ventricle 25 mm. The cavities of both ventricles were distended. The bronchi were free from obstruction. The lungs were normal though partly autolysed (right 620 g., left 620 g.). The pulmonary arteries contained no thrombi. The liver (2700 g.) was fatty and showed areas of autolysis, particularly in relation to the hepatic veins. The spleen (630 g.) was congested. The kidneys each weighed 380 g.; on the cut surface there were numerous

golden granules. The adrenal glands were autolysed; their total weight, with some fat attached, was 22 g. The thyroid (60 g.) contained a calcified nodule in the right upper pole. The pituitary appeared normal. The brain weighed 1275 g. and showed engorgement of the vessels over the cerebrum and congestion of the intra-cerebral small vessels.

Histologically, in the skin of the abdominal wall the collagen of the corium was broken up and thickened, and the appearances were those of lymphœdema. There was no fatty degeneration of the myocardial cells. The lungs, which were congested, showed evidence of slight emphysema. There was no bronchitis and the small branches of the pulmonary arteries were normal. The liver and kidneys showed fatty infiltration. Aggregates of fat in the kidney tubules were found to form the golden granules noted with the naked eye on the cut surface. The pituitary and hypothalamus were normal apart from some perivascular œdema in the latter.

Discussion

The clinical picture was that of cor pulmonale resembling especially emphysema heart failure, but none of the recognized causes of cor pulmonale was present. The embarrassment of respiratory expansion by the enormous mass of fat led to cardiac insufficiency, probably at the time of an upper respiratory tract infection six months before death. The infection cleared up but, when once cardiac failure had begun, the accumulation of œdema amid the adipose tissue of the body wall made a hard and unyielding cuirass. So the relatively slight restriction of respiration from fat alone was changed to a progressive immobilization of the chest from tensely œdematous fat. Increments of œdema further inflating the adipose tissues splinted the chest, the degree of heart failure increased and still more œdema of the parietes resulted. At the time of the patient's admission to hospital her vital capacity was already reduced to the volume of her tidal air, and treatment at that late stage failed to halt the self-aggravating process.

The great weight of the heart due to hypertrophy of both ventricles was a remarkable part of a general splanchnomegaly which likewise affected such lean organs as the kidneys. Left ventricular failure causing cor pulmonale reveals itself at necropsy in pulmonary œdema and the freedom of the lungs from œdema in this patient exonerates that ventricle. The bronchi and lungs showed no intrinsic disease other than mild emphysema and the pulmonary arteries showed no obliterative process.

The condition described here has an analogy in cardiorespiratory failure occurring in kyphoscoliosis. Sieker *et al.* (1955) have briefly reported similar cardiopulmonary failure in four patients with marked obesity. Pulmonary arterial pressures were moderately raised and pulmonary capillary pressures were normal. Reduction of weight brought improvement.

Summary

A case of extreme adiposity, leading to cardiorespiratory failure, is reported. When this had started, the adipose tissues of the body wall became tense with cardiac œdema and immobilized the chest, producing the clinical picture of cor pulmonale.

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STOKES-ADAMS ATTACKS IN ACUTE RHEUMATIC CARDITIS

BY

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In those exceptional cases of acute rheumatic carditis in which severe grades of heart block are met, the possibility of Stokes-Adams attacks must exist. This complication is, however, rarely seen and few examples have been recorded.

Schuster (1896) described the case of a boy aged 4 years who, during acute articular rheumatism, was found to have a pulse rate of 32 associated with fainting attacks. Stokes-Adams attacks were observed by Stern (1944) in a patient with acute pericarditis. Lukl and Cee (1953) noted syncopal attacks with complete heart block preceding the joint manifestations of acute rheumatic fever. Other cases have been described by Faulkner (1930), Salvesen (1932), Dumas (1938), Giraud *et al.* (1938), and Green and Bennett (1945). We describe a case that came under our own observation.

Case Report. The patient, a married woman, aged 22, was admitted to hospital with a history of a sore throat two weeks before, and for one week her right wrist had been swollen and painful. In the past she had rheumatic fever at the age of 7, and five subsequent attacks of fever and joint pains. She had two children, aged 6 and 5, without complication. Digitalis had been given intermittently for the last seven years, but not for several months prior to admission.

On examination the temperature was 101·5° F., and the right wrist was swollen, tender, red, and warm. No other joints were affected and there were no rheumatic nodules. The pulse rate was 100, irregular, and of small volume. The jugular venous pressure was not raised. The apex beat was in the fifth intercostal space just outside the mid-clavicular line. In the mitral area there was a loud first sound, a pansystolic murmur, a mitral opening snap, and a short mitral diastolic murmur. No early diastolic murmur was heard. The pulmonary component of the second sound was accentuated. Blood pressure was normal. The E.S.R. (Westergren) was 123 mm./1 hour. The cardiogram showed partial heart block where every third or fourth auricular beat was not conducted (Fig. 1A). Radiologically the heart was enlarged. An exacerbation of carditis with mitral stenosis and incompetence was diagnosed.

Progress. Symptomatic improvement followed salicylate therapy, but five days after admission the jugular venous pressure was raised 5 cm. above the sternal angle with the patient at 45°. There was no clinical evidence of pericardial effusion and 2 grains of digitalis leaf was given daily. The cardiogram again showed partial heart block with dropped beats every second, third, fourth or even fifth auricular beat not being conducted (Fig. 1B).

Eleven days after admission she suddenly became unconscious, but seven minutes later, after oxygen and artificial respiration she recovered with a good peripheral circulation and normal reflexes. The pulse rate was then 42, and a tentative diagnosis of a Stokes-Adams attack was made. Digitalis therapy was discontinued. During the night she had two further attacks which were epileptiform in character and she was given ephedrine hydrochloride. Later in the day a typical Stokes-Adams attack was witnessed by one of us, in which the patient first vomited, then became unconscious for twenty seconds, during which time no radial pulse could be felt and no heart sounds were heard on auscultation. Return to consciousness was heralded by a diffuse facial flush and a pulse rate of 70 to 80 for two to three minutes before returning to 40 a minute once more. She was given atropine sulphate (1/60 grain) four hourly, which raised the pulse rate to 80, but after three hours her pulse rate again returned to 40 to 50. Atropine dosage was altered to 1/100 gr. two hourly. No further Stokes-Adams attacks occurred. The cardiogram then (Fig. 1C) showed 2 : 1 heart block, and (Fig. 1D) complete heart block a week later. Later she reverted to partial

heart block with dropped beats; 12 days after this the cardiogram showed latent heart block with a P–R interval of 0·34 second, and after two months the P–R interval was normal.

One month after admission the joint pains had gone, the temperature was normal, and the E.S.R. was 35 mm./hour. An early diastolic murmur was heard on occasion at the left sternal edge. Two months after admission she was sent to a convalescent home, her E.S.R. having been below 10 mm./hour for three weeks.

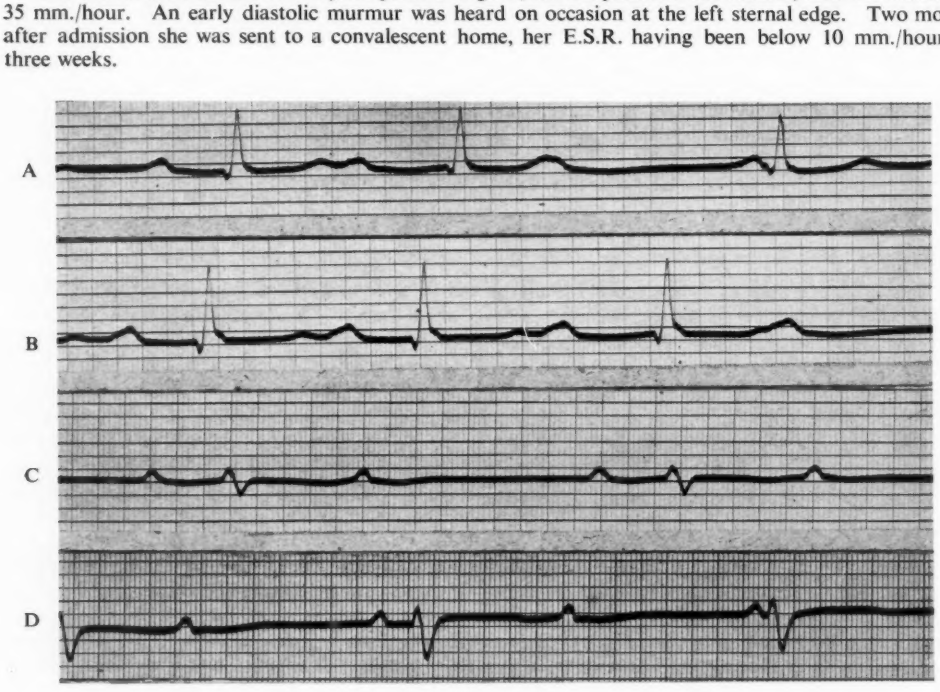

FIG. 1.—(A) and (B) Partial heart block with dropped beats, (C) 2 : 1 heart block, (D) Complete heart block.

Discussion

Complete heart block is rarely met with in rheumatic fever. Parkinson *et al.* (1920) recorded partial heart block in 15 out of 50 cases of rheumatic fever, 4 of which developed dropped beats. Once the acute rheumatic process has subsided the disorder of conduction usually disappears although paroxysmal complete heart block has been noted in association with Stokes-Adams attacks in patients with chronic carditis (Graybiel and White, 1936; Campbell, 1944). In practically all cases where Stokes-Adams attacks have been reported as a complication of rheumatic fever there was no previous rheumatic history with the exception of a woman aged 45 (Dumas, 1938) and the present case, in both of whom there was an established lesion of the mitral valve. The attacks were infrequent and occurred during the active phase of rheumatic carditis, usually over a period of not longer than 48 hours; recurrent attacks were, however, observed by Green and Bennett (1948) whenever their patient relapsed with pyrexia and joint pains. In those cases where serial cardiograms were available it was common to find partial heart block with dropped beats, 2 : 1 heart block, and complete heart block in no ordered sequence over a period of a few days and it was during this time that Stokes-Adams attacks occurred.

The cardiogram usually returned to normal within two to eight weeks. Apart from the presence of varying grades of heart block there seemed no further reason why Stokes-Adams attacks should occur in these cases. Digitalis may be a factor where severe grades of heart block occur

in acute inflammatory lesions of the myocardium, and in experimental animals Cushny (1925) observed that raising the temperature of the heart rendered them more susceptible to digitalis. Our patient had received digitalis folia, 1 grain twice daily, for six days preceding the Stokes-Adams attacks, and in two further cases digitalis had been administered (Dumas, 1938; Giraud, 1938). Although in the remaining six cases there is no mention of digitalis being used, it is possible that its administration may be of significance in the precipitation of Stokes-Adams attacks in acute rheumatic carditis.

Summary

A case of rheumatic fever is reported where transient complete and partial heart block was associated with Stokes-Adams attacks. There was eventual electrocardiographic recovery. This complication of rheumatic fever is unusual and only eight reports of similar cases were found. No convincing evidence as to the cause of the Stokes-Adams attacks was found on reviewing these cases.

We wish to thank Dr. Wallace Brigden for his permission to publish this case and for his helpful advice.

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ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

Effects of Restriction of Dietary Fat and Cholesterol upon Serum Lipids and Lipoproteins in Patients with Hypertension. F. T. HATCH, L. L. ABELL, and F. E. KENDALL. *Amer. J. Med.*, **19**, 48–60, July, 1955.

Working at the Goldwater Memorial Hospital (Columbia University), New York, the authors have taken advantage of the therapeutic use of the Kempner rice diet in the treatment of hypertension to study the effects of the drastic reduction of fat (to 3 g. per day) and complete elimination of cholesterol intake which this diet entails on the levels of lipoprotein and neutral fat in the serum.

During the control period the serum lipid levels in these hypertensive patients differed little from those in a series of healthy ambulatory subjects. Only during the administration of the unmodified Kempner diet was there a statistically significant reduction in the mean blood cholesterol level, and then by only 15%, that is, not below the normal range of values. Investigation of the behaviour of the different groups of serum lipoproteins showed no significant alteration in the concentration of the S_f 12–20 lipoprotein fractions, but a statistically significant increase (nearly double) in the concentration of the S_f 20–100 fractions during the period on the rice diet. All the changes seemed to depend on the restriction of fat rather than on the elimination of cholesterol, but even on the diet severely reduced in fat content some patients showed a lipæmia, with significant increase in the serum neutral fat content.

[These results suggest that simple dietary measures are unlikely to be of much help in the prevention or treatment of atheroma. Virtual elimination of fat from the diet produces only a small reduction in the serum lipid level.] *P. Hugh-Jones*

Paradoxical Action of Glyceryl Trinitrate (Nitroglycerin) in Coronary Patients. H. I. RUSSEK, K. F. URBACH, and B. L. ZOHMAN. *J. Amer. med. Ass.*, **158**, 1017–1021, July 23, 1955.

An investigation is reported from the United States Public Health Service Hospital, Staten Island, New York, of the effect of glyceryl trinitrate in 158 patients with coronary arterial disease who showed consistently positive changes in the electrocardiogram (ECG) following standard exercise (Master two-step test). Arterial hypertension was present in about 40% of the patients; 22 had had acute myocardial infarction and 51 complained of angina. The patients were given 0·4 mg. of glyceryl trinitrate 5 minutes before starting the Master two-step test. A normal response to the test was obtained in 105 patients, while 26 showed an improved response; 16 of these 131 patients, however, showed less dramatic improvement or even an abnormal response after receiving larger doses (0·6 to 1·2 mg.) of glyceryl trinitrate. No improvement in the ECG was observed in 11 patients, although 5 responded favourably to larger doses. In 16 cases there were more marked abnormalities in the ECG after exercise when glyceryl trinitrate was given than when it was not. *K. G. Lowe*

Angina Pectoris Induced by Fat Ingestion in Patients with Coronary Artery Disease. Ballistocardiographic and Electrocardiographic Findings. P. T. KUO and C. R. JOYNER. *J. Amer. med. Ass.*, **158**, 1008–1013, July 23, 1955.

To determine whether post-prandial lipæmia actually precipitates the syndrome of angina pectoris, 14 patients with coronary arterial insufficiency were given a fatty meal consisting of sweetened cream flavoured with cocoa (0·6 g. butter fat per lb. (1·3 g. per kg.) body weight). The turbidity of the plasma was taken as an index of post-prandial lipæmia. Typical attacks of angina were experienced by 6 of the patients; one of these with idiopathic hyperlipæmia had severe pain on 4 separate occasions about 3 hours after the fatty meal when lipæmia was maximum; in the other 5 patients maximum lipæmia and anginal attacks occurred about 4½ to 5 hours after the fatty meal. Some of the attacks were terminated by administration of glyceryl trinitrate and some by intravenous injection of small doses of heparin.

K. G. Lowe

A Three to Seven Year Postoperative Evaluation of 76 Patients with Severe Hypertension Treated by Thoracolumbar Sympathectomy. H. A. ZINTEL, A. M. SELLERS, W. A. JEFFERS, J. A. MACKIE, J. H. HAFKENSCHIEL, and M. A. LINDAUER. *Surg. Gynec. Obstet.*, **101**, 48–54, July, 1955.

This report from the University of Pennsylvania Hospital, Philadelphia, forms part of a larger programme whose ultimate aim is to compare the results of sympathectomy alone with those obtained by combined adrenalectomy and sympathectomy in the treatment of severe arterial hypertension. In the present paper the effect of sympathectomy alone is considered. Between 1947 and 1951 76 patients underwent 152 operations with only one operative death, an operative mortality of 0·6% and a patient mortality of 1·3%. All the patients had severe hypertension, about half of them fulfilling the criteria of Smithwick's Group IV. The follow-up period ranged from 3 to 7 years.

Survival-rate curves are presented in graphs for both series, and show that in each grade of disease operation conferred a considerable increase in survival time. The mortality for men in the follow-up period (49%) was almost three times that for women (18%). Of the 76 patients, 53 were alive at the time of the report. In over half (55%) of them the blood pressure was below 180/110 mm. Hg, the average reduction obtained in these survivors being 40/25 mm. Hg. Other analyses presented in tables show that renal function was not

improved by operation, whereas the electrocardiographic findings and heart size sometimes were. Congestive heart failure, angina pectoris, and headache usually did not return after operation. *C. J. Longland*

Correlation of Pulmonary Arteriolar Resistance with Pulmonary Vascular Changes in Patients with Mitral Stenosis before and after Valvulotomy. F. GOODALE, G. SANCHEZ, A. L. FRIEDLICH, J. G. SCANNELL, and G. S. MYERS. *New Engl. J. Med.*, **252**, 979–983, June 9, 1955.

It has been suggested by some workers that in the treatment of mitral stenosis severe pulmonary changes, in the form of alveolar fibrosis and intimal fibrosis in the small blood vessels, vitiate or even preclude the beneficial effects of valvotomy. The present authors take a more optimistic view, and at Massachusetts General Hospital have operated successfully in all types of case. In this paper they correlate the results of operation with the histological changes found in a biopsy specimen in each of 50 cases. The "pulmonary arteriolar resistance" was calculated in all cases before operation, and again some 5 to 28 months after operation in 16 of them. The area of the mitral orifice was also measured and the biopsy specimen taken from the anterior border of the left upper lobe of the lung.

In all but one of the 16 patients studied post-operatively there was a fall in pulmonary arterial pressure, and in all but 2 (in whom it had been very low) there was a fall in arteriolar resistance. The authors conclude that the poor correlation between the severity of the preoperative pulmonary resistance and the pathological changes in the lung indicates that vasoconstriction is an important factor in producing pulmonary hypertension in mitral stenosis. They consider that in most cases the increased pulmonary resistance is reversible and hence that relief of the stenosis by valvotomy should be undertaken whatever the severity of the preoperative hypertension.

Donald McDonald

Dynamics of the Circulation in Aortic Valvular Disease. R. GORLIN, I. K. R. MCMILLAN, W. E. MEDD, M. B. MATTHEWS, and R. DALEY. *Amer. J. Med.*, **18**, 855–870, June, 1955.

The authors have studied, at St. Thomas's Hospital, London, the dynamics of the circulation in 24 cases of aortic valvular disease, in 9 of which the effects of stenosis were preponderant, in 5 those of regurgitation, and in 10 there was evidence of both stenosis and regurgitation. The patients were studied both clinically and by cardiac catheterization; in 3 cases the aortic valve was also studied post mortem during simulated action produced by attaching to the heart a specially designed pump [not described in the paper]. Pressure gradients across the valves were then determined, cinephotographs of the valve in action taken, and the area of the valve orifice measured. The method of differentiation of the predominantly stenotic cases from those showing mainly regurgitation was based on the heart sounds, the brachial arterial pressure tracing, and fluoroscopy of the heart, the criteria adopted being shown.

The authors showed that symptoms due to pure stenosis appear when the area of the aortic-valve orifice is less than 0·5 sq. cm., and those due to combined stenosis and incompetence when the area is less than 1·5 sq. cm. Indirect assessment of the left ventricular pressure and pressure gradient across the valve in aortic stenosis suggests that these values are 200 to 250 mm. and 100 to 150 mm. Hg respectively. In cases both of stenosis and of incompetence the left ventricular stroke work was increased, but evidence of left ventricular failure was seen only on exercise, when an increase in the pulmonary capillary diastolic pressure occurred. The volume of regurgitation is reduced by an increase in heart rate, for then the diastolic period is shortened.

H. E. Holling

The Wide Patent Ductus Arteriosus. G. J. AITKEN. *Glasg. med. J.*, **36**, 175–186, June, 1955.

Among 98 patients with patent ductus arteriosus investigated at the Royal Infirmary, Glasgow, 18 were considered to have features characteristic of a wide ductus transmitting a large shunt from aorta to pulmonary artery. The large size of the ductus was confirmed at operation in all of the 16 patients so far subjected to surgery. The clinical features characteristic of a wide ductus were as follows: (1) a history of a marked degree of dyspnœa and of serious respiratory infections in childhood; (2) a pulmonary "systolic–diastolic" murmur instead of the usual Gibson (machinery) murmur [their distinction is not very clear]; (3) a widely disseminated systolic element in the murmur and thrill, which could be felt in the suprasternal notch; (4) a higher pulse pressure than usual; and (5) an apical diastolic murmur in more than half the group. In most of these cases also the left atrium was enlarged.

J. A. Cosh

Surgical Closure of Interatrial Septal Defects by Circumclusion. [In English]. T. SØNDERGAARD, H. GØTZSCHE, P. OTTOSEN, and J. SCHULTZ. *Acta chir. scand.*, **109**, 188–196, July 23, 1955.

After a concise review of the methods devised by various previous workers for closing interatrial defects the authors describe in detail their own method and present a report on 6 patients successfully treated at the Kommunehospital, Aarhus, Denmark. Essentially, the method consists in blunt dissection into, and development of, the cleavage plane which is present between the muscular walls of the right and left atria and which is filled with loose connective tissue. When this is completed the right index finger is inserted into the right atrium through the auricle and the extent of the defect explored. A curved blunt probe is placed at the upper end of the cleavage and, with very slight pressure, is guided along the lower edge of the defect until it appears at the lower end in the pad of fat situated between the atria and the coronary sinus. An oiled silk No. 10 suture is then secured to the tip of the probe and gently pulled back along the groove as the probe is withdrawn, the two free ends of the suture being tied over a piece of gelatin sponge at the lower end of the cleavage. As the suture is pulled tight the right index finger in the right atrium feels the defect becoming smaller and smaller and finally closing ("circumclusion").

The ages of the 6 patients subjected to this operation ranged from 4 to 33 years. All were improved by the operation, and subsequent cardiac catheterization in 4 of them revealed complete closure of the defect, with normal intracardial pressures. *C. A. Jackson*

The Physiological and Clinical Changes following Closure of Atrial Septal Defects by Atrio-septo-pexy. H. GOLDBERG and D. F. DOWNING. *Amer. Heart J.*, **49**, 862–879, June, 1955.

To study the effect on cardiac hæmodynamics of closure of an atrial septal defect, cardiac catheterization was carried out at Hahnemann Hospital, Philadelphia, before and after the performance of atrio-septo-pexy (suture of the right atrial wall to the margin of the defect) on 14 patients with this anomaly. Diagnosis was confirmed in all cases by cardiac catheterization and determination of the blood oxygen saturation; in only 2 cases was the catheter passed through the defect. Before operation all 14 patients had increased pulmonary blood flow, ranging from 6·2 to 31 litres per minute (1·4 to 8·7 times the systemic blood flow), and all had an intracardiac shunt from left to right, ranging from 3·0 to 27·6 litres per minute. In only 3 patients was the arterial oxygen saturation reduced, and none was cyanosed. In 8 cases there was pulmonary arterial hypertension but only 3 showed increased pulmonary resistance.

Postoperative studies showed that the left-to-right shunt had been eliminated in 11 cases, almost eliminated in one, moderately reduced in one, and unchanged in one. Associated with elimination of the shunt was a fall in pulmonary arterial pressure, though not always to normal levels. Elimination of the shunt was associated radiologically with a striking decrease in the pulmonary vascular markings and in the size of the cardiac silhouette. *K. G. Lowe*

Cardiovascular Surgery — International Symposium. Edited by Conrad R. Lam, M.D., foreword by Sir Russell Brock. Pp. xxix + 543. W. B. Saunders Company Ltd., London. Price 89*s*.

This volume contains the proceedings of the symposium on cardiovascular surgery held at the Henry Ford Hospital, Detroit, in March, 1955. There were 60 participants, many of them from countries outside the United States, and by means of papers and panel discussions the whole field of cardiovascular surgery, with the exception of the surgery of coronary disease, was covered. This volume gives an excellent account of the results achieved and work in progress on the surgery of congenital heart disease, mitral and aortic valvular disease, aneurysms and occlusive disease of the aorta. Recent work on the closure of atrial septal defects, controlled cross-circulation for direct vision intracardiac surgery, cardiac arrest, and hypothermia are also included. There are sections on diagnostic techniques and physiological studies. Apart from its obvious importance to the cardiac surgeon, this book will be of great interest to the cardiologist responsible for the selection of patients for cardiac surgery. *Graham Hayward*

Intracardial Surgery with the Aid of a Mechanical Pump-oxygenator System (Gibbon Type): Report of eight Cases. J. W. KIRKLIN, J. W. DUSHANE, R. T. PATRICK, D. E. DONALD, P. S. HETZET, H. G. HARSHBARGER, and E. H. WOOD. *Proc. Mayo Clin.*, **30**, 201–206, May 18, 1955.

A mechanical pump–oxygenator system was employed at the Mayo Clinic during intracardiac surgery on 8 patients aged 4 months to 11 years with the following congenital cardiac lesions: ventricular septal defect (4 cases), atrial septal defect (1), a common atrio-ventricular canal (2), and Fallot's tetralogy (1). Severe pulmonary hypertension was present in all the cases except the last. Very careful selection of patients for this type of operation is necessary and the criteria for this are outlined.

Four of the 8 patients survived and were well at the time of the report. One died during operation, possibly from an inadequate circulating blood volume, but the remaining 3 deaths occurred postoperatively and did not appear to be related to the perfusion process. *J. A. Cosh*

Klinische Elektrokardiographie. VON DR. M. HOLZMANN, Zürich. 3., erweiterte und verbesserte Auflage, 1955. XII, 688 Seiten, 303 Abbildungen, 1 farbige Tafel, Gr.-8°, Ganzleinen DM 80. GEORG THIEME VERLAG.

The third edition of Clinical Electrocardiography is some forty pages longer than the second, but has the same number of illustrations. The plan of the book is, in general, much the same as before. The standard three leads still are prominently to the fore, and are often the only curves shown. It is time this changed, and more selective illustrations were used. The theory of circus movement is still conspicuous, Prinzmetal receiving a few lines at the end of the section. The curves of ventricular hypertrophy need rather more modern discussion. The cardiograms throughout are clear and adequate. The discussion is sound and conservative. There is little about treatment, but hardly enough if it is to come in at all. Altogether a sound and satisfactory book, which deals with all aspects of the subject very adequately. *Terence East*

Das postthrombotische Syndrom. TH. HALSE. 1954. Verlag Dietrich Steinkopff, Darmstadt. 114 pages. 34 illustrations.

The Post-thrombotic Syndrome is a monograph that deals with the pathogenesis, diagnosis, treatment, and avoidance of the consequences of acute thrombosis of the veins in the legs. The first part contains observations on the importance of these diseases from the point of view of social medicine, and shows how much disability has resulted in the past. The use of the antithrombotic remedies in acute phases has vastly reduced the invalidism. The anatomy and physiology are well reviewed. There are good photographs of phlebograms. These show how useful they can be in demonstrating the importance of deep vein thrombosis. This little book is a sound and interesting review of a subject often neglected as dull and disappointing. *Terence East*

The Members of the British Cardiac Society dedicate this number to Crighton Bramwell on the occasion of his election as an Honorary Member of the Society.

CRIGHTON BRAMWELL

BY
MAURICE CAMPBELL

Crighton Bramwell has been a prominent member of the Cardiac Society and its predecessor, the Cardiac Club, for more than thirty years. He was the first member elected in 1923 to join the original fifteen who had started the Cardiac Club in 1922, and was Secretary from 1928–32. He was Chairman in 1931 and in 1936–37, when it fell to him to preside at the special meeting that changed the small Cardiac Club into the larger Cardiac Society, and again in 1955–56.

After resident appointments, Bramwell was appointed Medical Registrar at the Manchester Royal Infirmary—the only one in those days—and in 1926 he was appointed to the staff, a position he held till 1954. In his early days he worked with A. V. Hill, McSwiney, Downing, and McDowall on the pulse wave velocity and arterial elasticity, and the results were published in the *Proceedings of the Royal Society* (*B***93,** 298 and *B***94**, 450, 1921–23), in *Heart* (**10**, 233 and 289, 1923), and in the *Quarterly Journal of Medicine* (**17**, 225, 1924). He found that the pulse wave velocity was about 6 metres a second in young adults, and more in older patients and in those with a raised diastolic pressure because of the decreased arterial elasticity. This work is extended using different methods by Shirley Smith and Conway in the present number.

In 1928 he wrote on aneurysmal dilatation of the left auricle (*Quart. J. Med.*, **21**, 187) commenting on the fibrosis and loss of muscle in the auricular wall and on the amount these patients were able to do in spite of the large heart, and with Ellis on quinidine therapy in auricular fibrillation (*Lancet*, **2**, 960). For some years he worked on the mechanics of the circulation in athletes. The final paper (*Quart. J. Med.*, **24**, 329, 1931) is still interesting to read but difficult to summarize: many of the marathon runners had hearts that were large by ordinary standards, and he thought this was partly because of training and partly because a naturally large heart might be useful for severe efforts.

He has always been interested in the treatment and prognosis of patients with heart disease during pregnancy (*Lancet*, **1**, 629, 1935, and *Brit. med. J.*, **1**, 897, 1953) and his conclusions were expressed in 1938 in his book with Longson, *Heart Disease and Pregnancy*. In 1939 he wrote in this journal with Morgan Jones on the alcoholic beri-beri heart, and in 1941 on the collateral circulation in coarctation of the aorta, one of the classic descriptions of this that has not been bettered. He discussed the clinical features and prognosis of coarctation in his St. Cyres lecture (*Brit. Heart J.*, **9**, 100, 1947).

With Morgan Jones again (*Brit. Heart J.*, **6**, 129, 1944) he wrote about acute left auricular failure in mitral stenosis—a concept that had been put forward by Gallavardin but neglected for several years though it has now taken the important place it deserves in the symptomatology of mitral stenosis.

He has always been interested in physical signs and has written on gallop rhythm and on the pulse: his Lumleian lectures dealt with *The Arterial Pulse in Health and Disease* (1937). But he has dealt with a wider field also, as is well shown by his book with King—*The Principles and Practice of Cardiology*.

Bramwell has been a great clinical teacher and a fine example of the physician with a speciality who has maintained his interest in general medicine. His good judgment and wide, balanced knowledge have led to a great demand for his services as an examiner and special lecturer. In the

Carey Coombs Memorial lecture at the University of Bristol he reviewed in masterly fashion the subject of rheumatic heart disease, 1924–54 (*Lancet*, **1**, 214, 1955).

During his time at the Manchester Royal, his department grew from a small one for taking electrocardiograms to a larger one with its own patients and research workers and laboratories. In 1940 Bramwell became part-time Professor of Systemic Medicine and in 1946, when the post became a whole-time one, he gave this up to become part-time Professor of Cardiology—the first such appointment in this country. His department became the University Department of Cardiology and its present buildings were opened in 1949. These achievements have taken place in close liaison with other departments and without friction and show something of his character. An excellent colleague and chief, he has been reasonable and fair in discussion, ready to give advice, and wise and quick in making decisions when they are needed.

Dr. Fergus R. Ferguson in the *Manchester University Medical School Gazette* wrote as follows. " Thirty-six years ago I first met Crighton Bramwell. Following his service in the First World War he had spent a month fishing in far north Melvich before joining us as a resident at the Manchester Royal. Melvich was to have very happy associations for him, for it was there he met his wife, Elsa, whose wisdom and companionship have meant so much to him.

" Bramwell was house physician to George Murray, who discovered the thyroid treatment for myxœdema, and I was with that delightful little man and wise clinician Albert Ramsbottom. Bramwell had the greatest respect and affection for both these men. At that time, the first cases of epidemic encephalitis were appearing in this country and Jack Bramwell and I had many consultations on these strange and new clinical pictures. . . .

" And what of the man himself, always courteous, always controlled: even under provocation his voice is firm but never raised. In appearance, cultured and distinguished, with his tall rather willowy body, a little stooped, advancing a little sideways with the forefoot going down well after the heel—we shall always remember him and welcome him at the Manchester Royal."

His work always came first, but two great interests survived and occupied most of his spare time. Fishing was one of these, which he has sometimes managed to combine with his outside examining. Before the war he had a lovely old house at Baguley, outside Manchester, with a large garden, where he could always be found as soon as his work was finished. During the war he began spending more weekends in the Lake District and has now settled there in a cottage near Ambleside, where he is enthusiastically making a new rockery and garden.

From its beginning to the present day Crighton Bramwell has been an active and valuable member of the British Cardiac Society. His influence has been directed to its scientific aims and to maintaining the good fellowship essential to its healthy growth. He is admired and greatly liked by his fellow members who, this year, elected him with acclamation as an Honorary Member.

A CLINICO-PATHOLOGICAL STUDY OF CORONARY DISEASE

BY

P. J. D. SNOW, A. MORGAN JONES, AND K. S. DABER

From the Departments of Cardiology and Pathology, University of Manchester

In a previous paper (Snow *et al.*, 1955) the pathological findings in the hearts of twenty-five patients with coronary disease were described. In the present paper these findings, together with those in an additional seven patients, are correlated with the clinical features.

Material. Thirty-two patients were studied, all with clinical evidence of ischæmic heart disease. Those in whom hypertension or valvular lesions may have contributed to the ischæmic symptoms were not excluded. Sixteen of the patients had been under the care of the Department of Cardiology and all had been observed personally by one of us; 11 had been under the care of other units of Manchester Royal Infirmary, and 5 had been admitted to Crumpsall Hospital, Manchester. Only cases with a full clinical history were included in the series, which was not consecutive.

Symptoms occurring within three months of death were the main basis of this study since up to this time the age of a myocardial infarct can be estimated pathologically and correlated chronologically with the clinical events.

At necropsy the coronary arteries were injected with a radiopaque medium and radiographed to locate all occlusions; the myocardium was then serially sectioned and all lesions examined histologically by the technique previously described (Snow *et al.*, 1955).

Results

Age and Sex Distribution. The series included 29 men and 3 women whose ages ranged from forty-one to seventy-eight, with a maximum incidence in the sixth decade. This accords with the age incidence of coronary disease found by other authors (Master *et al.*, 1939; and Friedberg, 1950).

The Symptoms of Coronary Occlusion. Of the 53 occlusions only seven occurred without infarction and all these seven occlusions were in arteries supplying previously infarcted areas. In none of these seven were any clinical symptoms associated with the occlusions but, since it is not possible to assess the age of occlusions accurately, these findings should be regarded only as suggesting that occlusion without infarction may be asymptomatic.

The Symptoms of Myocardial Infarction. Seventy-seven infarcts were present of which 52 were recent (i.e. less than three months old) and could be accurately correlated with the symptoms. The other 25 infarcts were healed and of indefinite age so that chronological correlation was impossible.

Of the 52 recent infarcts, 28 (54%) corresponded with episodes of prolonged cardiac ischæmic pain, two (4%) with the onset of angina of effort and two (4%) with the onset or aggravation of dyspnœa. Nineteen infarcts (36%) gave rise to no apparent symptoms, and one occurring while the patient was comatose is excluded.

Although accurate chronological correlation with the symptoms was impossible in the case of the 25 healed infarcts, it was interesting to note that thirteen could have corresponded with the onset of angina of effort, three with the aggravation of existing angina, six with prolonged cardiac pain, and one with the onset of dyspnœa. In two no symptoms were recorded.

Asymptomatic and Atypical Infarcts. Twenty-three (45%) of the 51 recent infarcts whose symptoms were known were unassociated with prolonged pain. These infarcts were distributed between fifteen hearts in eleven of which other infarcts that were associated with typical prolonged

pain were also present. An analysis of these lesions was made in an attempt to discover reasons for the lack of typical symptoms.

No correlation could be found between the symptoms and the size or site of infarcts, or whether painless infarction preceded or followed clinically recognizable infarction when this co-existed in the same heart. When the infarcts were grouped according to their precipitating causes (i.e. with or without occlusion), however, a difference was apparent (see Table I).

TABLE I

CLINICAL SIGNS OF RECENT CARDIAC INFARCTS

Clinical manifestations	Recent infarcts with occlusions		Recent infarcts without occlusions	
	No.	Percentage	No.	Percentage
Prolonged cardiac pain	21	70	7	33
Sudden onset of angina	1	3	1	5
Sudden onset of dyspnœa	1	3	1	5
Asymptomatic	7	23	12	57
Total*	30	100	21	100

* Excludes an infarct that occurred in a comatose patient.

Thirty of the 51 recent infarcts were due to occlusion and 21 (70%) of these caused prolonged pain. On the other hand, 21 were either completely unrelated to occlusion or else arose by extension from previous infarcts without further occlusion (Snow *et al.*, 1955) and of these, only seven (33%) caused prolonged pain. Although these numbers are small, this difference is unlikely to have arisen by chance ($\chi^2=5{\cdot}33$: $p\simeq 0{\cdot}02$).

The Pathological Significance of Prolonged Cardiac Pain. Thirty-one episodes of chest pain or discomfort judged to be of cardiac origin and of over half an hour's duration occurred within three months of death. Up to this time the age of an infarct may be assessed with a reasonable degree of accuracy, hence permitting correlation with the symptoms. In twenty-eight of these episodes, infarcts of corresponding ages were found at necropsy.

In two instances of prolonged pain without corresponding evidence of infarction possible explanations were obvious. In one case two episodes of pain occurred on the fifteenth and seventeenth days before death and at autopsy an infarct fourteen to eighteen days old was found: a difference of two days in the ages of two confluent infarcts would not be detectable when both were over two weeks old and it is possible that both episodes of pain were associated with infarction. In another the episode of pain occurred the day before death and, although no corresponding infarct was found post mortem, histological changes of infarction might have appeared had death been postponed.

The remaining episode of pain occurred two months before death but no corresponding infarct could be found post mortem. This is the only clear exception to the general conclusion that cardiac pain lasting more than half an hour is an indication of myocardial infarction.

The Pathological Significance of the Onset or Aggravation of Angina of Effort. There were 24 episodes of the sudden onset or aggravation of angina of effort. Unfortunately for purposes of accurate correlation, only four of these occurred within three months of death. In three of these four cases angina was the only symptom of coronary disease. In two the onset of angina coincided with the histologically determined ages of the infarcts. In the third angina began three weeks before death but no corresponding infarct was found. In the one case in which angina beginning three months before death was followed by an attack of prolonged pain on the day before death, there was a small healed infarct that could have been three months old.

Of the 20 instances in which angina began more than six months before death, two had no infarcts that could have corresponded with them, but in all the rest healed infarcts were present, and since prolonged cardiac pain was absent in all but two cases until two months before death, the onset or aggravation of angina of effort was the only recorded clinical manifestation of these infarcts.

Discussion

Despite numerous clinico-pathological studies there is still disagreement about the clinical manifestations of coronary occlusion and myocardial infarction, and the pathological significance of angina of effort and prolonged cardiac pain at rest. This uncertainty is reflected in the present confused terminology, and as Levy (1948) stated " accurate terminology is not mere quibbling, for it promotes clear thinking and intelligent therapeutic procedure." Freedberg *et al.* (1948) pointed out that the recognition of the various types of cardiac pain has been accompanied by a diversity of opinion concerning the applicable diagnostic terms. There is still, for example, disagreement as to the correct designation for an attack of prolonged cardiac ischæmic pain and the terms coronary thrombosis, coronary occlusion, and myocardial infarction have all been used, often apparently indiscriminately (Editorial, *Brit. med. J.*, **1**, 1499, 1951).

The Symptoms and Diagnosis of Coronary Occlusion. At one time coronary occlusion was believed to be the cause of the clinical syndrome of " coronary thrombosis," but many now believe that the symptoms are due to myocardial infarction rather than coronary occlusion.

Friedberg (1950) stated, without quoting pathological evidence, that the acute onset of angina of effort may be due to an occlusion without an ensuing infarct, whereas Blumgart *et al.* (1940) concluded that occlusions alone do not cause any symptoms and it is the resultant infarct, if any, that is responsible for the clinical manifestations. Master and his colleagues (Master *et al.*, 1941 and 1944; Master, 1944 and 1946) on the other hand have repeatedly maintained that it is possible to distinguish infarcts due to occlusions from those due to extra-coronary factors by clinical and electrocardiographic criteria. There is thus a diversity of opinion as to the clinical manifestations and diagnostic criteria of coronary occlusions.

Two points must be made from the present observations. First, unlike infarcts occlusions cannot be accurately " aged," though they can be classified as recent, healing, or old, and attempts to corfelate symptoms with them chronologically might be fallacious. Secondly, in this study occlusions without infarction were uncommon and when present were apparently asymptomatic, but this conclusion is subject to the reservation about assessing the age of the occlusion.

None the less, infarction without occlusion may have somewhat different clinical manifestations from infarction due to occlusion, since only 7 of 21 infarcts without occlusions or due to extensions of previous infarction without new occlusion caused typical prolonged cardiac pain, compared with 21 of 30 infarcts due to occlusions. These proportions are almost identical with those of Gorham and Martin (1938), and Master and his colleagues also observed that pain was usually severe when infarction resulted from occlusion and was mild or absent when infarction was due to " coronary insufficiency."

These authors considered that the syndrome of severe prolonged cardiac pain with shock and a cardiogram showing abnormal Q waves, elevated RS–T segments and inverted T waves was diagnostic of infarction due to occlusion in 95 per cent of cases, but they were comparing the clinical and cardiographic manifestations of infarcts that they believed to be due to occlusion with infarcts due to gross general coronary insufficiency, which are usually subendocardial and associated with fairly characteristic cardiographic signs, thus constituting a distinct type of infarct. They have not taken into account the fact that the commoner transmural infarcts may also occur without occlusions. In the present series, the electrocardiographic changes were similar whether infarction was due to occlusion or not.

The suggestion of Blumgart *et al.* (1940) that the presence of an occlusion may be surmised when infarction occurs while the work of the heart is not increased, was not borne out by the present study in which infarcts occurred without occlusions in hearts of normal size while the patients were at rest

and in the absence of valvular lesions or hypertension. This seems to us to be a point of considerable interest, but we cannot put forward any satisfactory explanation. For reasons that we hope to discuss in a subsequent paper, we believe that it is not simply due to missing the presence of coronary occlusions.

It is concluded that when solitary occlusions occur they appear to be asymptomatic, and there appear to be no criteria by which they may be recognized clinically. We do not think that it is justifiable to diagnose coronary occlusion clinically and, with Freedberg *et al.* (1948), we would like to see this clinical diagnosis discarded.

The Symptoms of Myocardial Infarction. Our observations conform to the general impression that the clinical manifestations of myocardial infarction may vary from prolonged cardiac pain at rest to brief pain on effort only, while in other cases pain may be replaced by dyspnœa or even by no apparent symptoms. Our figures emphasize the comparatively high proportion of cases (46%) in which infarction fails to cause typical prolonged pain.

The problem of painless infarction is an important one and raises several questions. How often does it occur? Why is pain absent? Is the prognosis poor? The large and rather confused literature on this subject has been concerned almost exclusively with the first two questions and agreement has not been reached on either.

The Frequency of Painless Infarction. The published figures for the frequency of painless infarction vary widely because there has been little agreement on the interpretation of the term painless, and some authors refer to the number of episodes of coronary thrombosis which may not have meant infarction, while others refer not to the number of painless infarcts but to the cases in which they occurred, without allowing for the fact that both painful and painless infarcts may occur in the same heart. Further, the criteria for recognizing infarction have usually been purely clinical without pathological confirmation. In these circumstances it is not surprising that the reported incidence of painless infarction should vary from 1 to 61 per cent (Table II).

TABLE II

PERCENTAGE OF PAINLESS INFARCTS

Authors	Percentage painless	Cases or infarcts	Criteria for recognition of infarcts
Parkinson and Bedford, 1928	2	Cases	Post mortem
Levine and Brown, 1929 ..	48	Cases	Post mortem
Davies, 1932	40	Cases	Post mortem
Howard, 1934	6	Cases	Not mentioned
Saphir *et al.*, 1935	38	Cases	Post mortem
Bruenn *et al.*, 1936	61	Cases	Post mortem
Boyd and Werblow, 1937 ..	33	Cases	Post mortem in some; others not stated
Kennedy, 1937	4	Infarcts	Post mortem
Bean, 1938	28	Infarcts	Post mortem
Gorham and Martin, 1938	42	Infarcts	Post mortem
Master *et al.*, 1938	60	Cases	Post mortem
Babey, 1939	1	Cases	E.C. only, leads not stated
Gross and Engelberg, 1940	25	Cases	Post mortem
Pollard and Harvill, 1940 ..	8	Cases	E.C. and several post mortems
Rosenbaum and Levine, 1941	3	Cases	Clinical or post mortem *
Stroud and Wagner, 1941 ..	26	Cases	E.C. or post mortem
Kugel, 1945	3	Cases	None given
Chambers, 1946	21	Cases	Clinical and E.C.
Mintz and Katz, 1947 ..	3	Cases	Clinical or post mortem *
White, 1947	3	Cases	Post mortem
Billings *et al.*, 1949	10	Cases	Clinical or post mortem *
Hipp *et al.*, 1949	7	Infarcts	E.C.
Landman *et al.*, 1949 ..	11	Cases	Post mortem
Papp, 1952	5	Cases	E.C.
Roseman, 1954	2	Cases	E.C. or post mortem

* Number not specified.

In the present series 36 per cent of infarcts were completely without symptoms while 45 per cent were without typical prolonged pain and, since only cases with adequate clinical records and detailed pathological data were used, these results are probably comparatively accurate in this group of cases.

The designation asymptomatic, while correct as far as could be established, was used subject to certain reservations, for it obviously is not possible to question the patient soon after an apparently asymptomatic infarct has occurred and the possibility that vague, mild symptoms were present cannot be denied, but the distinction between an asymptomatic infarct and one with mild atypical symptoms is of no practical importance since neither would be diagnosed except by chance electrocardiography. A much more serious difficulty is the frequency with which patients appear to develop some degree of amnesia for the initial symptoms in severe infarction; although they may complain of severe pain when seen during the attack this is often denied when they are questioned a week later.

Speculations on the Explanation of Painless Infarction. Several explanations for the occurrence of painless infarction have been put forward but without much evidence. These speculations are summarized below, together with the main evidence against them.

	Suggested explanation	Reasons against
Libman (1919)	Hyposensitivity of patient.	Painful and painless infarction may occur in the same heart.
Herrick (1931)	" Silent areas " of myocardium.	No correlation found between site of infarct and occurrence of pain.
Levine and Brown (1929), Herrick (1931), and Blumgart *et al.* (1941).	Gradual occlusion with gradual muscle necrosis.	Gradual occlusion may cause painful infarct.
Davis (1932)	Acute occlusion with absolute ischæmia.	Sutton and Lueth (1930) invariably produced pain by acute occlusion.
Gorham and Martin (1938) ..	Pain depended on the increased tension in wall of vessel proximal to occlusion.	Coronary occlusion has no effect on arterial pressure proximal to it. (Wiggers and Cotton, 1938.)

The occurrence of painless infarction is unquestioned and, whatever its incidence, its existence is a challenge to try to discover the reason or reasons for the absence of pain in some cases. Most attempts to do this have been made by trying to correlate known clinical factors (cardiac enlargement, hypertension, arrhythmia, etc. (Evans and Sutton, 1956)) or pathological observations (site, extent, collateral circulation, previous infarction, etc.) with the presence or absence of pain. Work on these lines has not led to any convincing conclusion and it may be that the problem must be approached from a broader point of view. The difficulty in understanding painless infarction is due to the widely held assumption that a degree of ischæmia sufficient to cause infarction must also cause pain, and it has then to be explained why some infarcts do not conform to this general rule.

Various attempts have been made to explain painless infarction without discarding this assumption, but we do not consider them satisfactory. In our view, insufficient attention has been paid to the importance of *duration* of ischæmia as opposed to its *intensity*. Experimentally, complete occlusion of a major coronary artery will not cause infarction provided that occlusion is relieved within twenty to thirty minutes (Tennant and Wiggers, 1935; Blumgart *et al.*, 1941). In pain, on the other hand, the intensity of the ischæmia alone determines whether pain occurs, for even momentary occlusion is sufficient to cause pain (Sutton and Lueth, 1930) but if pain continues for over half an hour it is, from our own observations, almost invariably accompanied by infarction. Contrary therefore to the usual assumption, it is conceivable that a grade of ischæmia insufficient to produce pain may, if it persists for long enough, lead to infarction.

The Possible Dangers of Painless Infarction. Since patients are unlikely to rest after an asymptomatic infarct, the risks of extension or rupture of the infarct and ventricular fibrillation may be increased, and Bourne (1939), Le Roy and Snider (1941), Rosenbaum and Levine (1941), Boas (1942), Dressler (1944), Mintz and Katz (1947) and Billings *et al.* (1949), all concluded that infarcts with atypical symptoms have a higher mortality. In our clinical cases, infarcts that were not precipitated by occlusions were often painless and it is interesting that infarcts without occlusions

accounted for a high proportion of cases of sudden death that have been studied. (These are not included in this series and will be reported elsewhere.)

The Diagnostic Significance of Prolonged Cardiac Pain and the Onset of Angina of Effort. There has been surprisingly little attempt to establish the pathological significance of the onset of angina despite its long clinical recognition, although there is now a general opinion that it may often signify coronary occlusion without infarction (Friedberg, 1950). In our series isolated occlusions seldom occurred and when they did so were asymptomatic so this view may need revision.

There is, however, some evidence to suggest that the onset of angina may indicate infarction with or without coronary occlusion. Both Obrastzow and Straschesko (1910) and Herrick (1912) reported cases in which myocardial infarcts proved at autopsy were associated with the onset of angina, and more recently Bourne (1939), Le Roy and Snider (1941), Boas (1942), Dressler (1944) and Wade and Morgan Jones (1951) all pointed out that the onset of angina may signify infarction, and mentioned the danger attached to this presentation owing to the risk of sudden death from failure to recognize and treat the infarct. Riseman and Brown (1937) found that the blood sedimentation rate was increased in 50 per cent of cases with angina of recent onset, and believed this to be due to myocardial damage.

Our observations confirm that the acute onset of angina may be the clinical counterpart of infarction but do not indicate how often this is so, or how such cases can be distinguished from those without infarction. From the practical point of view, however, it seems advisable to regard the recent acute onset of angina as an indication that infarction has occurred.

The uncertain significance of an attack of prolonged cardiac pain is reflected in the present confused terminology for the terms coronary thrombosis, coronary occlusion, and myocardial infarction have all been used apparently synonymously. Possibly because of the uncertain significance of such pain there has been a tendency to belittle its importance when it occurs without electrocardiographic evidence of infarction. There is now, however, an increasing body of opinion that regards prolonged cardiac pain as usually significant of infarction (Blumgart *et al.*, 1940; Master *et al.*, 1944; Freedberg *et al.*, 1948; Friedberg, 1950; and Wood, 1950). Strong confirmation of this view was afforded by the present study in which there were 31 episodes of cardiac pain lasting for over half an hour and at least 28 of these were found to have corresponding infarcts post mortem. Cardiac pain of this duration is therefore quite a reliable indication that infarction has occurred.

Summary

The symptoms of 32 patients with coronary disease have been correlated with the post-mortem findings. No evidence was found of coronary occlusion causing symptoms, which were always attributable to myocardial infarction.

In particular, prolonged cardiac pain of over half an hour duration was found to be a very reliable indication of myocardial infarction.

A high proportion of infarcts, however, did not give rise to any recognizable symptoms and the possible reasons for this are discussed.

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THE EFFECTS OF ADRENERGIC-BLOCKING AGENTS ON THE PULMONARY CIRCULATION IN MAN

BY

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The pulmonary blood vessels are richly inervated with fibres derived from both the sympathetic and parasympathetic nervous systems (Larsell, 1951; Mitchell, 1956) but attempts to demonstrate vasomotricity have yielded conflicting results. If the sympathetic fibres have a pulmonary vasomotor action, it might be anticipated that the administration of an adrenergic-blocking agent would have some demonstrable effect, especially if injected directly into the pulmonary artery. In 1953 Meriel *et al.* (1953) reported a fall in the pulmonary arterial pressure in normal subjects, in patients with mitral stenosis, and in a single case of primary pulmonary hypertension, following the injection of hydergine into the pulmonary artery through a cardiac catheter. (Hydergine consists of equal parts of the three hydrogenated alkaloids of ergot, dihydroergocornine, dihydroergocryptine, and dihydroergocristine.) They concluded that it exerted a direct action on the vasomotor system of the lungs. Using a similar technique Halmagy *et al.* (1953*b*) reported that hydergine had no effect on pulmonary dynamics: they found that dihydroergotamine, when injected into the pulmonary artery, caused a rise in pulmonary arterial systolic pressure and resistance, and concluded that this drug was capable of producing pulmonary vasoconstriction. Similar observations and conclusions regarding dihydroergotamine were reported by Halmagy *et al.* (1953*a*).

If adrenergic-blocking agents have any effect on the pulmonary circulation, then the manner in which they act has far-reaching implications. It seems important, therefore, to re-examine the action of such an agent, and our purpose is to report the results of seven observations in which hæmodynamic measurements were made following the injection of hydergine into the pulmonary artery through a cardiac catheter and four more in which priscol (2-benzyl-2-imidazoline) was injected. In two further observations priscol was administered orally.

Material and Methods. The observations were made on thirteen patients selected at random. Nine suffered from mitral stenosis alone and two from mitral stenosis complicated in one by incompetence and in the other by aortic stenosis. One patient suffered from pulmonary heart disease and one from slight pulmonary stenosis.

Cardiac catheterization was performed in the usual way and an indwelling needle placed in the brachial artery. Pressures were recorded by means of a capacitance manometer and intra-thoracic pressures referred to a point 5 cm. below the sternal notch. Mean pressures were obtained by electrical filtration. In two cases (155 and 158) the systemic pressure was recorded simultaneously with the pulmonary arterial pressure. Cardiac outputs were estimated by the direct Fick procedure, the expired air being analysed on Haldane's instrument and blood gases by the Van Slyke-Neil manometric method. Vascular resistances were calculated from the following formulæ and expressed in c.g.s. units:

$$\text{Total Pulmonary Resistance (T.P.R.)} = \frac{(PA_m - 5) \times 1332}{\text{C.O. in ml./sec.}}$$

$$\text{Pulmonary Vascular Resistance (P.V.R.)} = \frac{(PA_m - PCV_m) \times 1332}{\text{C.O. in ml./sec.}}$$

$$\text{Peripheral Resistance} = \frac{BA_m \times 1332}{\text{C.O. in ml./sec.}}$$

where C.O. = cardiac

output, PA_m=mean pulmonary arterial pressure in mm. Hg, PCV_m=mean pressure recorded with catheter tip wedged in peripheral lung fields in mm. Hg, and BA_m=mean brachial artery pressure in mm. Hg.

In ten cases basal estimations of cardiac output, pressure, and resistance were made. A dose of hydergine or priscol was then injected down the cardiac catheter into the main stem of the pulmonary artery over a period of two minutes. Continuous pressure recordings were made for the next six minutes, a further output estimation being made between the fourth and sixth minutes. In one observation, following the basal estimations, the subject performed graded work on a bicycle ergometer, the output, pressures, and resistances being estimated during the fifth to seventh minute of work. This was considered long enough for a steady state to be obtained. After a period of rest hydergine was injected through the catheter and the work repeated with further estimations during the fifth to seventh minutes. It was considered unjustifiable to wedge the catheter repeatedly to measure the P.C.V. pressure on account of the risk of causing pulmonary infarction.

In the remaining two observations priscol was administered orally. The procedure varied only in that the second output estimation was not taken until 15–20 minutes after administering the drug.

RESULTS

Table I shows the findings in six observations following the injection of various doses of hydergine through the cardiac catheter into the main stem of the pulmonary artery: there is no consistent effect upon the cardiac output, the pulmonary arterial pressure, or the total pulmonary resistance, irrespective of the initial levels. With the exception of Case 101 in which there was an increase of 24 beats a minute, there was also no effect upon the heart rate. The systemic resistance was

TABLE I

THE EFFECT OF HYDERGINE ON THE PULMONARY CIRCULATION AFTER INJECTION INTO THE PULMONARY ARTERY

Case No.	Age and sex	Rhythm	Dose in mg.	State	Pulse rate	O_2 consumption (ml./min.)	B.A. O_2 content (vols. %)	P.A. O_2 content (vols. %)	Cardiac output (l./min.)	P.A. mean (mm. Hg)	Total pulmonary resistance (c.g.s. units)
91	31 F	S	0·15	B	90	269	16·7	13·4	8·1	41	355
				A	90	246	16·7	13·2	7·0	35	343
100	35 M	A.F.	0·30	B	94	208	17·7	12·5	4·0	33	560
				A	90	243	17·7	12·9	5·1	37	517
101	45 F	S	0·30	B	90	177	16·4	13·0	5·2	19	220
				A	114	185	16·4	12·4	4·6	26	354
102	41 M	A.F.	0·40	B	180	353	17·2	12·2	7·0	54	560
				A	174	280	17·3	12·6	6·0	53	647
107	35 F	S	0·50	B	100	159	14·8	10·9	4·1	57	1002
				A	96	198	14·7	9·2	3·6	54	1009
155	34 F	S	0·60	B	86	235	13·1	9·6	6·7	32	323
				A	85	236	13·2	9·3	6·0	32	360

S=Sinus rhythm. A.F.=Auricular fibrillation. B=Basal. A=After injection. B.A.=Brachial artery. P.A.=Pulmonary artery.

calculated simultaneously only in Case 155; there was a fall from 826 to 560 dynes/sec./cm.$^{-5}$ after injecting 0·6 mg. of hydergine although the T.P.R. was virtually unaltered (Fig. 1).

Table II shows the effect of 0·6 mg. of hydergine injected into the pulmonary artery upon the pattern of the pulmonary vascular response to effort in a case of moderately severe mitral stenosis

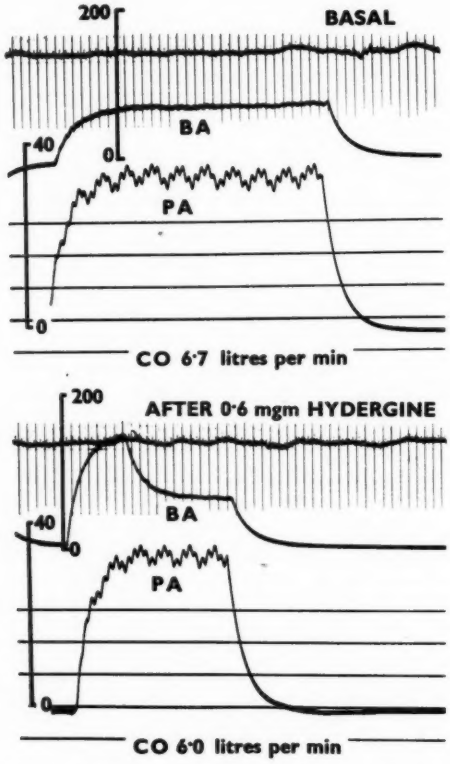

FIG. 1.—The effect of 0·6 mg. hydergine on brachial (BA) and pulmonary (PA) arterial pressures in mm. Hg after injection into the pulmonary artery.

with a low initial pulmonary vascular resistance. Both before and after hydergine the same amount of exercise produced an identical increase in the pulmonary vascular resistances. The systemic resistance remained unchanged.

Table III shows the effect of priscol injected into the pulmonary artery, in four cases, in varying dosage. Irrespective of dose there was an invariable increase in heart rate of from 9 to 24 beats a minute. There were no consistent changes in cardiac output and, with two exceptions, the alterations in pulmonary arterial pressures and resistances were so slight as to be insignificant. In Case 135 there was a fall in total pulmonary resistance from 470 to 236 dynes/sec./cm.$^{-5}$. This was brought about by a fall in pulmonary arterial pressure and a rise in cardiac output, and at the same time the heart rate rose by 16 beats a minute. In Case 93 there was a striking increase in total pulmonary resistance from 1115 to 2540 dynes/sec./cm.$^{-5}$ brought about by a rise in mean pulmonary arterial pressure from 78 to 113 mm. Hg and a fall in cardiac output from 5·3 to 3·4 l./min. More

TABLE II

THE CIRCULATORY RESPONSE TO EXERCISE BEFORE AND AFTER HYDERGINE IN A PATIENT WITH MITRAL STENOSIS (CASE 158)

State	Pulse	O_2 consumption (ml./min.)	A-V O_2 diff. (vols. %)	Cardiac output (l./min.)	P.A. pressure (mm. Hg) S D M	P.C.V. (mm. Hg)	Pulm. arteriol. resist. (c.g.s. units)	Total pulm. resist. (c.g.s. units)	Systemic pressure (mm. Hg) S D M	Peripheral resistance (c.g.s. units)
Rest ..	69	270	5·15	5·25	47 21 31	25	91	396	115 63 58	880
Exercise ..	90	492	7·15	6·8	80 35 56	—	—	600	121 54 71	840
Exercise and hydergine 0·6 mg. into P.A. ..	95	500	7·20	6·9	83 32 56	—	—	592	113 52 70	810

P.C.V. = Pulmonary capillary venous pressure. S = Systolic. D = Diastolic. M = Mean. P.A. = Pulmonary artery.

detailed analysis of this response (Fig. 2) shows that although the maximum increase in heart rate of 24 beats a minute occurred within 2 to 3 minutes, the pulmonary arterial pressure continued to rise until the fourth minute. Between the fifth and seventh minutes, when the response was at its height, the patient was very dyspnœic.

Administered orally, 50 mg. of priscol appears to have no effect on circulatory dynamics (Table III). In Case 149 the cardiac output was unusually low on both estimations and in consequence the total pulmonary resistance was remarkably high. This is largely due to a very low oxygen consumption. It was felt that this was possibly erroneous but no fault could be found in the mouthpiece, valves, connective tubing, or Tissot spirometer.

DISCUSSION

The dosage of hydergine used was of the same order as that employed by Halmagy *et al.* (1953*b*) and also by Meriel *et al.* (1953). Barcroft and Swan (1953) found that 0·6 mg. i.v. of either dihydroergocornine or hydergine was sufficient to cause peripheral vasodilation with a considerable increase in skin blood flow, while Gibbs (1952) observed that as little as 0·3 mg. i.v. caused a fall in systemic blood pressure. We also found that 0·6 mg. produced a fall in systemic blood pressure (Fig. 1) and it is probable that this is a fully effective dose.

We can find no evidence that hydergine is a pulmonary vasodilator. There is no constant effect, irrespective of the initial total pulmonary resistance. The failure to block or otherwise modify the anticipated increase in pulmonary resistance on effort in Case 158 is also against the concept that hydergine acts upon the pulmonary vasomotor system. It is possible that this type of response to effort, which occurs in some cases of mitral stenosis, may be independent of active vasomotor narrowing, having its origin in the increased rigidity of structurally abnormal vessels and the decreasing fluidity of blood in small-bore tubes (Eliasch, Wade, and Werko, 1952), but it is unlikely that this is a wholly satisfactory explanation when the resting vascular resistance is normal. We are therefore unable to agree with Meriel *et al.* (1953) that hydergine has a specific pulmonary vasodilator effect; or, as they claim, that it will serve to differentiate " functional " from " irreversible " narrowing of the pulmonary arterioles in mitral stenosis. In one case (101) the total pulmonary resistance rose by 60 per cent but this was the only case in which the heart rate increased, and it is possible that this shortening of diastolic filling time may have been the reason. Our observations support those of Halmagy *et al.* (1953*b*), namely, that hydergine has no constant effect on the cardiac output, the pulmonary arterial pressure, or the pulmonary resistance.

Halmagy *et al.* (1953*a*) reported that dihydroergotamine acted as a pulmonary vasoconstrictor. Ergotamine is known to exert a direct action on smooth muscle and, although an adrenergic-blocking agent, it acts, by virtue of this direct effect on vascular smooth muscle, as a vasoconstrictor (Goodman and Gilman, 1955). This undesirable side effect is less marked in ergotoxine and is further reduced by hydrogenation. Thus hydrogenated ergotoxine (hydergine) no longer possesses an overall

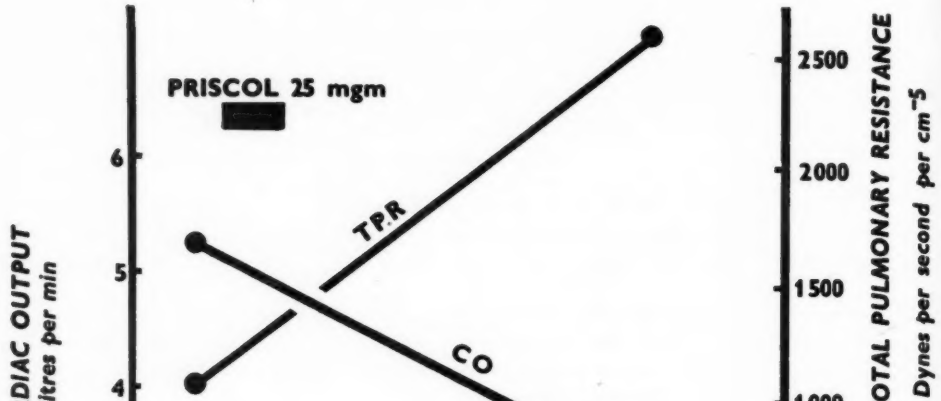

FIG. 2.—The circulatory response to injection of 25 mg of priscol into the pulmonary artery of a patient with mitral stenosis.

vasoconstrictor effect although dihydroergotamine still does. It is probably this direct action on the smooth muscle present in the walls of pulmonary arteries greater than 100 μ in diameter that is responsible for the vasoconstrictor effect observed by Halmagy *et al.* (1953*a*). There seems to be no justification for regarding this effect as evidence for the participation of the sympathetic nervous system in the genesis of established or labile pulmonary hypertension.

Priscol is also an adrenergic-blocking agent but has more undesirable side effects than hydergine, such as tachycardia, flushing, and conjunctival injection (Wakim *et al.*, 1950; Barcroft and Swan, 1953; Goodman and Gilman, 1955). We selected it for trial on account of the claim by Dresdale

TABLE III

THE EFFECT OF PRISCOL ON THE PULMONARY CIRCULATION

Case No.	Age and sex	Disease	Dose in mg.	Route of admin.	State	Pulse rate	O_2 consumption (ml./min.)	B.A. O_2 content (vols. %)	P.A. O_2 content (vols. %)	Cardiac output (l./min.)	P.A. mean (mm. Hg)	Total pulmonary resistance (c.g.s. units)
64	52 M	Cor Pul.	25	P.A.	B	97	225	14·8	11·1	6·1	34	386
					A	110	220	15·8	11·5	5·1	29	376
93	34 M	M.S.	25	P.A.	B	72	210	12·2	8·2	5·3	78	1115
					A	96	177	12·3	7·1	3·4	113	2540
135	48 F	M.S.	12·5	P.A.	B	114	221	17·1	12·9	5·3	36	470
					A	130	353	16·6	12·6	8·8	31	236
140	24 F	Slight P.S.	17·5	P.A.	B	66	276	15·3	12·0	8·4	8	24
					A	75	370	15·4	12·0	10·9	7	15
148	41 F	M.S., M.I.	50	Oral	B	70	232	17·5	12·5	4·6	63	1000
					A	80	301	17·2	11·4	5·2	61	860
149*	41 F	M.S., A.S.	50	Oral	B	135	99	14·95	6·4	1·15	68	4560
					A	135	85	14·15	5·9	1·03	68	5700

Cor Pul.=Cor pulmonale. B.A., P.A.=Brachial or pulmonary artery. A.S., M.S., P.S.=Aortic, mitral, or pulmonary stenosis. B=Basal. A=After administration of drug. M.I.=Mitral incompetence. C.O.=Cardiac output.

* Case 149 had atrial fibrillation: all the others had normal sinus rhythm.

et al. (1954) that when injected into the pulmonary artery it possesses a unique relaxant effect on the pulmonary arterioles in primary pulmonary hypertension, a disease characterized by a primary increase in pulmonary vascular hindrance (Wade, 1954). Dresdale *et al.* (1954) also reported a similar effect in a case of atrial septal defect complicated by pulmonary hypertension. Administered by the same route, we found the effect to be variable. Thus, in two cases there was no change, in one (Case 135) there was an appreciable fall and in the other (Case 93) there was a sharp rise in pulmonary arterial pressure and resistance, and a fall in cardiac output (Fig. 2); for several minutes the patient's condition caused anxiety. In a case of severe mitral stenosis with gross pulmonary hypertension previously investigated we observed a similar response to the intra-pulmonary arterial injection of 25 mg. of priscol, also with considerable embarrassment to the patient. (This case is not included in the series on account of failure to obtain satisfactory output estimations.) It might be thought that the associated tachycardia, by reducing diastolic filling time, could be an important factor, but this mechanism could only act by raising the mean left atrial, and therefore the pulmonary capillary pressure. The osmotic pressure of the blood, approximately 35 mm. Hg, limits the extent to which the capillary pressure can rise and active vasoconstriction has to be invoked to explain the large increase in total pulmonary resistance. A rise in left atrial pressure, acting through an unknown receptor-effector mechanism, might well cause a vasoconstrictive response in the pulmonary arterioles, but the temporal disproportion between the rise in pulse rate and pulmonary arterial pressure (Fig. 2) is against this explanation. It seems more probable that priscol has an inconstant direct effect upon arterial smooth muscle. It is important to recognize that this effect may occur and that intravenous or intra-arterial priscol therapy may therefore be dangerous in cases of mitral stenosis with severe pulmonary hypertension.

Conclusions

We have found that the adrenergic-blocking agents hydergine and priscol, when injected into the pulmonary artery, have no constant effect on pulmonary vascular dynamics, irrespective of the initial level of the total pulmonary resistance. There is, therefore, no evidence that, in the cases studied, the pulmonary vascular pattern was dependent on the excitor function of sympathetic nerves. In one case of severe mitral stenosis with gross pulmonary arterial hypertension, priscol caused a sharp rise in pulmonary arterial pressure and resistance and a fall in cardiac output, the patient becoming apprehensive and dyspnœic. We have encountered this type of response once previously in a similar case. We consider that it is due to a direct effect of priscol on arterial smooth muscle and we suggest that intravenous or intra-arterial priscol may be dangerous in this type of case. Oral priscol in a dose of 50 mg. appears to be without effect.

Summary

The results of eleven observations are reported in which measurements of the cardiac output and pulmonary pressures were made before and after the injection into the pulmonary artery of one of the adrenergic-blocking agents hydergine (equal parts of the three hydrogenated alkaloids of ergot, dihydroergocornine, dihydroergocryptine, and dihydroergocristine) or priscol (2-benzyl-2-imidazoline). In two further observations priscol was administered orally.

Hydergine has no appreciable effect, irrespective of the initial level of the pulmonary resistance. Priscol has a varying effect and, in one case of severe mitral stenosis with gross pulmonary hypertension caused anxiety by producing a sharp rise in pulmonary resistance and a fall in cardiac output. It is suggested that this is due to a direct effect on pulmonary arterial smooth muscle. By mouth, priscol appears ineffective.

The results yield no evidence that the sympathetic nervous system is concerned in the maintenance of the pulmonary vascular pattern irrespective of whether the pulmonary resistance is normal or raised.

We thank our patients who, without exception, were willing to co-operate in our observations. We also thank Dr. Morgan Jones for his interest and help.

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MITRAL STENOSIS WITH VERY HIGH PULMONARY VASCULAR RESISTANCE AND ATYPICAL FEATURES

BY

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A rise in pulmonary arterial pressure is almost invariable in severe mitral stenosis. In many patients it is slight or moderate but in a small proportion the pulmonary circulation reacts with extreme elevation of pulmonary vascular resistance and pulmonary arterial pressure. Some of these patients show the usual features of mitral stenosis but others present a difficult diagnostic problem, for many of the classical signs and symptoms of mitral stenosis may be absent or modified owing to the hindrance to blood flow proximal to the pulmonary capillary bed. From our experience we believe that between five and ten per cent of patients found to require mitral valvotomy show these atypical features and this agrees with the incidence (7·6%) found by Wood (1954).

The purpose of this paper is to describe the clinical and other features of six such patients and to discuss the results of surgery in five of them.

Methods. The six patients all attended the Department of Cardiology, Manchester Royal Infirmary. They were graded functionally, using the New York Heart Association's classification (1939). The history was elicited in detail and examination made jointly by the authors. Each patient was submitted to routine fluoroscopy and films were taken in the postero-anterior and right and left anterior oblique positions. The films were analysed by the method of Wade *et al.* (1952). Cardiographic examination consisted of standard leads, augmented unipolar limb leads, and præcordial leads V3R to V6 using Wilson's central terminal.

Five patients were subjected to cardiac catheterization and this was carried out in the usual way. Pressures were recorded with a capacitance manometer or saline monometer (Case 1) with reference to a point 5 cm. below the sternal notch. Blood gases were analysed by the Van Slyke–Neil manometric method and expired air in the Haldane apparatus. Cardiac output was estimated by the direct Fick procedure. One patient, following basal estimations, performed graded work on a bicycle ergometer, cardiac output, pressures, and resistances being estimated during the fourth to sixth minute of work; this was considered long enough for a steady state to be obtained (Eliasch *et al.*, 1952; Donald *et al.*, 1954). Cardiac catheterization was repeated in three patients, a variable interval after mitral valvotomy.

Vascular resistances were calculated from the following formulæ and expressed in units as dynes sec./cm.$^{-5}$.

Total pulmonary resistance (T.P.R.) $=(PA._m-5)\times 1332/C.O.$ in ml./sec.

Pulmonary vascular resistance (P.V.R.) $=(PA._m-PCV._m)\times 1332/C.O.$ in ml./sec.

Peripheral resistance $=BA._m\times 1332/C.O.$ in ml./sec.

Where $PA._m$ = mean pulmonary artery pressure in mm. Hg.

$PCV._m$ = mean pressure with catheter tip wedged in peripheral lung field.

$BA._m$ = mean brachial artery pressure in mm. Hg.

Clinical Characteristics

Symptoms. All patients were functionally in Grade IV. A striking feature was the rapidity of progress from slight to almost complete incapacity. Thus, the time from onset of symptoms

to total incapacity was seven years or less in all and under three years in three patients. In all, the limiting symptom was progressive breathlessness on exertion but by the time they were seen in hospital their chief complaint was of exhaustion and a feeling of inability to make any physical effort. Several patients complained: " My legs feel like lumps of lead." Cold extremities and a feeling of permanent fatigue were noted by three patients. Two experienced syncopal attacks on exertion. Four were orthopnœic, three had recurrent hæmoptysis, but only one had attacks of paroxysmal dyspnœa. All suffered attacks of congestive heart failure before admission to hospital and three were extremely resistant to the usual forms of treatment. Failure occurred in each patient when they were still in sinus rhythm and only one (Case 6) had any obvious precipitating factor (pneumonia).

Signs. The facial appearance of five of these patients was striking, with a deep cyanotic malar flush. The extremities were cold and arterial blood pressure tended to be low with a small pulse pressure. The most prominent physical signs—present in all cases—were those of pulmonary arterial hypertension and right ventricular hypertrophy, namely *a* waves in the jugular venous pulse (Fig. 1), a systolic lift over the right ventricular outflow tract, a right ventricular heave, and a loud split second pulmonary heart sound. All patients had sinus rhythm on admission to hospital but one developed auricular fibrillation before mitral valvotomy (Case 3) and one (Case 5) developed paroxysmal auricular fibrillation during the last week of his life.

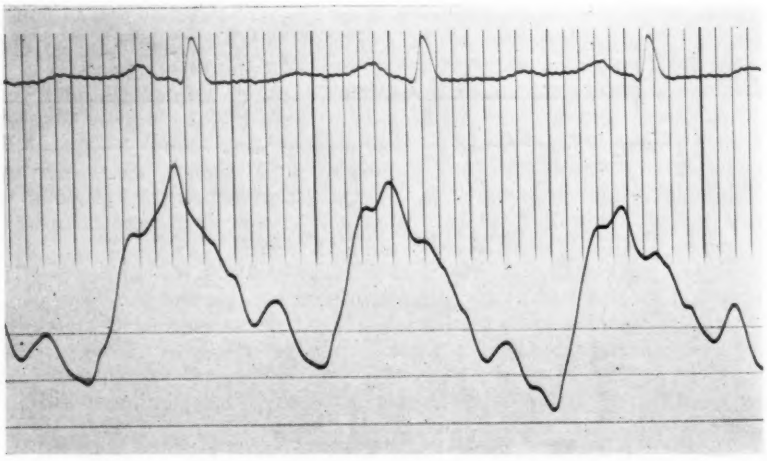


FIG. 1.—Synchronous recordings of lead II of the electrocardiogram and the jugular venous pulse in Case 6, showing prominent atrial waves.

The mitral first heart sound was of normal intensity in three patients and increased in three. Calcium was visible on fluoroscopy in the mitral valve in the three patients with a normal first heart sound. The opening snap was not heard in five patients and was doubtful in the other.

Murmurs were notable only for their softness or absence. A soft mid-diastolic murmur was audible in the mitral area in three patients with presystolic accentuation in one: in the other three no diastolic murmur was heard (see Table I). A systolic murmur was present in three patients, at the apex in one and in the left parasternal area in two. A soft diminuendo diastolic murmur was audible down the left sternal border in three and was thought to be due to pulmonary incompetence.

All patients had evidence of pulmonary congestion as judged by the presence of moist râles at the lung bases and two suffered pulmonary infarction, one on several occasions (Case 5).

TABLE I

PHYSICAL SIGNS

Case No.	Mitral first heart sound	Mitral diastolic murmur	Mitral presystolic murmur
1	N	−	−
2	A	+	−
3	N	−	−
4	A	+	−
5	N	−	−
6	A	+	+

N=Normal. A=Accentuated.
All patients had a right ventricular heave, prominent atrial waves in the jugular venous pulse, and sinus rhythm.

Details of three patients help to illustrate the history and diagnostic difficulties that these patients may present.

Case 3. A woman, aged 31, had chorea at the age of 13 and a heart murmur was discovered when she was 28, during an uneventful pregnancy. She was first seen complaining of fairly sudden onset of breathlessness on exertion two years before with rapid deterioration since. Twelve months before she had had to stop work on account of exhaustion and was unable to climb a flight of stairs. At this time she had two syncopal attacks on exertion, when she collapsed unconscious for several minutes while walking slightly faster than usual. Her legs always felt very heavy and she complained of cold extremities. Ankle swelling first occurred about nine months before, and two weeks before she was seen she developed pleural pain and hæmoptysis which was thought to be due to pulmonary infarction. She was orthopnœic but had no paroxysmal dyspnœa. When first seen, she was found to have considerable congestive heart failure.

Case 1. A man, aged 29, had served in the armed forces for 4 years during the war. In March, 1950, he first noted breathlessness on exertion and hæmoptysis following an influenzal illness. By September, his incapacity was severe and he complained of permanent fatigue, weariness, and complete exhaustion on any physical exertion. His condition thereafter remained static until January, 1953, when he had two syncopal attacks on exertion lasting about two minutes, and a month later further hæmoptysis and for the first time some ankle swelling. In April he began having repeated small hæmoptyses, became orthopnœic, and had several attacks of paroxysmal cardiac dyspnœa necessitating admission to hospital elsewhere. He was admitted to this hospital in July, 1953. He was a well built man, orthopnœic and breathless on slight exertion. The heart rhythm was normal. Prominent atrial waves were visible in the jugular venous pulse and there was a parasternal heave suggesting right ventricular hypertrophy. The mitral first heart sound was of normal intensity but the pulmonary second sound was loud and split. A loud systolic murmur was audible at the lower end of the sternum but no mitral diastolic or presystolic murmur was present. There was no opening snap. Blood pressure was 110/90 mm. Hg. A few crepitations were present at the lung bases and the liver was palpable two finger breadth's below the right costal margin. There was no peripheral œdema. A clinical diagnosis of pulmonary hypertension of unknown ætiology was made and the presence of mitral stenosis was not established until the radiological and catheterization findings were known.

Case 5. A man, aged 29, gave a history of rheumatic fever when he was eight years old but had little incapacity until two years before his first attendance. At this time he became progressively more breathless on exertion and felt completely exhausted. Three months before he was seen he developed congestive heart failure and had recurrent hæmoptyses necessitating admission to another hospital. He was admitted to this hospital with a recurrence of gross congestive heart failure. At this time there was sinus rhythm, prominent atrial waves in the jugular venous pulse, and a right ventricular heave. The mitral first heart sound was of normal intensity and there was no opening snap. The pulmonary second heart sound was loud and split. There was a soft apical systolic murmur but no diastolic or presystolic murmur. There were râles at the lung bases and signs of pulmonary infarction at the right base.

A diagnosis of pulmonary hypertension, probably secondary to mitral stenosis, was made. Unfortunately his heart failure showed no response to rigid salt restriction, digitalis, mercurial diuretics, and a kation exchange resin, and he never became fit enough to catheterize. He developed multiple

areas of pulmonary infarction, and paroxysms of auricular fibrillation and died five weeks after admission. Autopsy examination revealed a heavily calcified, tightly stenosed mitral valve with right ventricular hypertrophy and pulmonary arterial atheroma.

Electrocardiography. The cardiogram invariably showed the pattern of right ventricular hypertrophy and clockwise rotation of the heart, with high-voltage R waves and inverted T waves extending from V3R to V3 or V4. A typical electrocardiogram is shown in Fig. 3A.

Radiology. The right ventricle was considerably enlarged in all patients. The left ventricle was slightly enlarged in only one. The left atrium was moderately enlarged in two and only slightly enlarged in the remainder.

Extreme prominence of the main branches of the pulmonary artery was present in all patients whereas vascular markings in the peripheral lung fields were " great " in only one, " moderate " in three, and " slight " in two. Horizontal lines due to interlobular œdema (Kerley, 1951) were present in three patients, doubtful in two, and absent in the other. Calcium was visible on fluoroscopy in the region of the mitral valve in three patients.

Fig. 2 shows the chest radiograph of Case 6 with extremely prominent pulmonary conus and main branches of the pulmonary artery, but little or no peripheral pulmonary congestion and no lines due to interlobular œdema in spite of severe mitral stenosis.

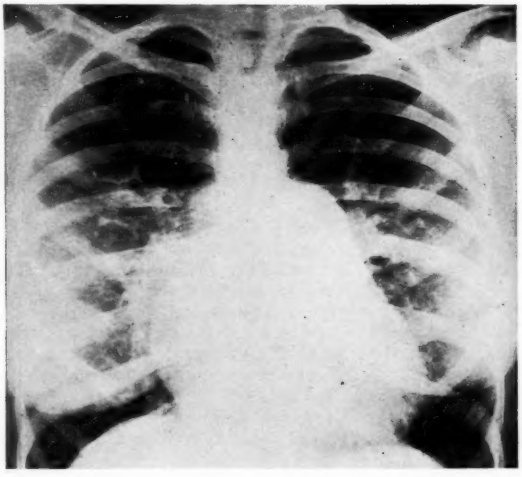


FIG. 2.—Chest radiograph of Case 6, showing prominent pulmonary conus and main branches of the pulmonary artery, but only slight peripheral pulmonary congestion in spite of severe mitral stenosis.

CARDIAC CATHETERIZATION

The results of cardiac catheterization are summarized in Table II. Severe pulmonary hypertension was present in all five patients—the mean pulmonary artery pressure being over 70 mm. Hg on each occasion. The remarkably high pressure of 177/90 mm. (mean 123 mm. Hg) was recorded in Case 6.

P.C.V. pressure was obtained in three patients and was found to be raised, moderately in two and severely in one. This last patient was the only one in the group who had paroxysmal cardiac dyspnœa. The oxygen saturation of mixed venous blood was low (60% or below) and arteriovenous oxygen difference high in four patients in whom it was measured. Cardiac output was low (2·6, 4·0, and 3·2 litres/min.) and total pulmonary resistance was greatly increased (2580, 1310, and

TABLE II

CARDIAC CATHETERIZATION RESULTS

Case No.	P. A. pressure			Mean P.C.V. pressure (mm. Hg)	Per cent O_2 saturation		A-V O_2 Difference (vols. %)	Cardiac output (l./min.)	Cardiac index	Total pulmonary resistance (dynes/sec./cm.$^{-5}$)	Pulmonary vascular resistance (dynes/sec./cm.$^{-5}$)
	Systolic	Diastolic	Mean		P.A.	B.A.					
1			74	35	46	96	10·4				
2	126	64	89	24	60	91	7·2	2·6	1·7	2580	2000
3	99	57	77	—							
4	125	44	72	25	60	90	6·1	4·0	2·8	1310	910
6	177	90	123	—	53	95	8·0	3·2	2·1	2930	—

P.A.=Pulmonary artery. P.C.V.=Pulmonary capillary venous. B.A.=Brachial artery.

2930 units) in three patients in whom these measurements were made; and in view of the low oxygen saturation of mixed venous blood and severe pulmonary hypertension in Case 1 pulmonary resistance must also have been very high in this patient. Arterial oxygen saturation was slightly reduced in two and was normal in two patients.

The effect of exercise was observed before valvotomy in one patient (Case 4; Table III). During exercise a striking increase in total pulmonary resistance occurred (1310 to 2450 units) and was associated with a fall in cardiac output from 4·0 to 3·0 litres/min. and a rise in mean pulmonary artery pressure from 72 to 94 mm. Hg.

TABLE III

EFFECT OF EXERCISE ON VASCULAR DYNAMICS IN CASE NO. 4

	Mean P.A. pressure (mm. Hg)	Per cent O_2 saturation		A-V O_2 difference (vols. %)	Cardiac output	Cardiac index	Total pulmonary resistance	Pulmonary vascular resistance
		P.A.	B.A.					
Basal	72	60	90	6·1	4·0	2·8	1310	910
Exercise	94	32	92	11·5	3·0	2·1	2450	

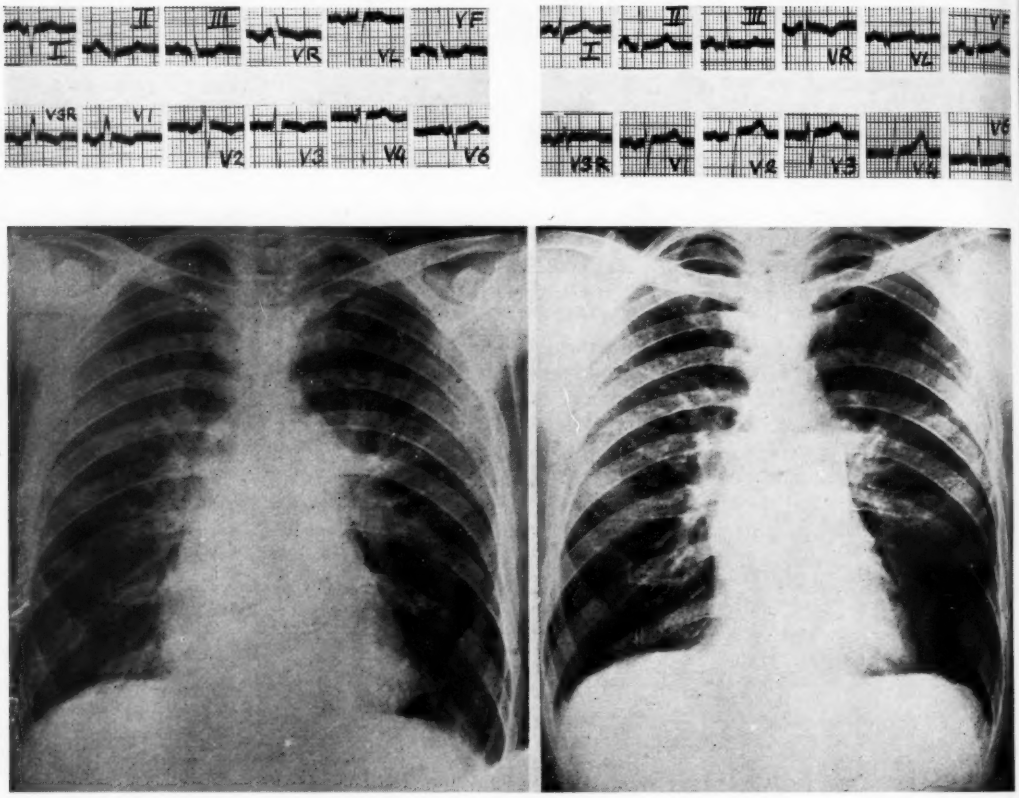
SURGICAL TREATMENT

Mitral valvotomy was performed in five patients—in four by Mr. Frank Nicholson and in one (Case 6) by Mr. Gordon Jack. Some operative findings and results are shown in Table IV. Tight mitral stenosis was a constant finding—the valve size being estimated as less than 0·5 cm. in four patients and less than 1 cm. in the other. Moderate and heavy calcification of the mitral valve was present in two patients (Cases 1 and 3).

The surgeon judged that a good " split " of the mitral valve was obtained in four patients, and a moderate one in the fifth (Case 3). One (Case 2) died twelve hours after operation without regaining consciousness: permission for a necropsy was not obtained and the exact cause of death was not ascertained.

Three patients have shown striking subjective and objective improvement as a result of valvotomy. Signs of pulmonary hypertension have disappeared, heart size has diminished, and clinical and radiological pulmonary congestion has improved (Fig. 3). The electrocardiogram has returned to normal in one patient (Fig. 3) and is still improving in two.

Two of these patients, from being completely incapacitated with resistant congestive heart failure requiring low sodium diet and diuretics, have improved to functional grade I and now lead a normal life without any specific treatment. The other patient is now in Grade II. The fourth (Case 6) who was operated on quite recently is already functionally improved and radiologically



A B

FIG. 3.—Chest radiographs and electrocardiograph of Case 1. (A) Before mitral valvotomy, and (B) 32 months after, showing reduction in heart size and pulmonary congestion. The cardiogram had returned to normal.

the proximal branches of the pulmonary arteries are less prominent. The post-operative period was smooth in the four surviving patients and the early disappearance of orthopnœa was a noticeable feature in two of them. Auricular fibrillation occurred in one patient but normal rhythm was restored with quinidine sulphate on the twelfth day after operation.

TABLE IV

FINDINGS AT AND RESULTS OF SURGERY

Case No.	Valve calcification	Valve size (cm.)		Functional grade after operation
		Before	After	
1	Heavy	$>\frac{1}{2}$	2·5	I
2	None	$>\frac{1}{2}$	3	Died
3	Moderate	$>\frac{1}{2}$	3	II
4	None	$>\frac{1}{2}$	2·5	I
6	None	>1	3	III

Cardiac catheterization was performed in Cases 4 and 6 four weeks after operation and in Case 1 thirty-two months after, and the results are shown in Table V. In Cases 1 and 4 dramatic reduction in pulmonary arterial pressure (22 and 40 mm. Hg) and P.C.V. pressure (14 and 8 mm. Hg) was found (Fig. 4). Pulmonary resistance in Case 1 was found to be only slightly increased at post-operative catheterization and although it was not measured before, it must by implication have been high. The pulmonary artery in the third patient (Case 6) was not catheterized and although

TABLE V

POST-OPERATIVE CARDIAC CATHETERIZATION

Case No.	P.A. pressure			Mean P.C.V. pressure (mm.Hg)	Per cent O_2 saturation		A-V O_2 difference (vols. %)	Cardiac output (l./min.)	Cardiac index	T.P.R. (dynes/sec/cm.$^{-5}$)	P.V.R. (dynes/sec/cm.$^{-5}$)
	Systolic	Diastolic	Mean		P.A.	B.A.					
1 Pre-op.			74	35	46	96	10·4				
Post-op			22	14	71	96·2	5·1	4·7	2.8	292	146
4 Pre-op.	125	44	72	25	60	90	6·1	4·0	2·8	1310	910
Post-op	66	24	40	8	—	—					
6 Pre-op.	177	91	123	—	53	94·6	8·0	3·2	2·1	2930	—
Post-op	R.V. 140				R.V. 63·5		5·1				

R.V. = Right ventricle.

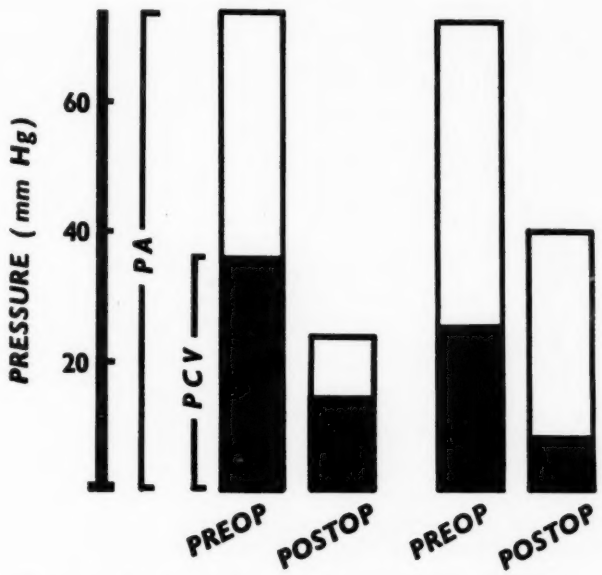


FIG. 4.—Histogram, showing fall in mean pulmonary artery and pulmonary capillary venous pressure after mitral valvotomy in two patients (Cases 1 and 4).

right ventricular systolic pressure showed a fall to 140 mm. Hg, severe pulmonary hypertension persisted. The oxygen saturation of right ventricular blood had, however, increased and the arterio-venous oxygen difference had fallen, suggesting that cardiac output was probably higher and pulmonary resistance lower than previously.

Discussion

Mitral stenosis usually runs a long course with an average duration from onset of symptoms to total incapacity of from seven (Wood, 1954) to fifteen years (Olesen, 1955); the symptoms are mainly ascribable to congestion of the pulmonary capillary bed, namely breathlessness on exertion, paroxysmal dyspnœa, hæmoptysis, and orthopnœa. By contrast our six patients deteriorated rapidly after the onset of symptoms and all reached total incapacity within seven years, the duration of symptoms being three years or less in four of them. Their symptoms consisted of fatigue and exhaustion as well as breathlessness on exertion, and exertional syncope occurred in two patients. Despite the invariable tight mitral stenosis, orthopnœa, paroxysmal cardiac dyspnœa, and hæmoptysis may be absent. None of our patients described anginal pain on exertion though for many years this symptom has been known to occur in patients with mitral stenosis complicated by pulmonary atherosclerosis: Stuckey (1955) suggested that it occurs as a result of inadequate coronary blood flow during exercise due to a fixed, low cardiac output. Low cardiac output was found in all three cases in which it was estimated; further, it may remain fixed or fall on exertion and this is associated with increased pulmonary vascular resistance (Case 4; Donald *et al*, 1954). A striking feature is the early onset of congestive heart failure and its resistance to intensive treatment.

The physical signs in this group are quite different from those found in most patients with mitral stenosis. In addition to obvious signs of pulmonary hypertension our patients had a striking appearance with malar cyanotic flush, cold cyanosed extremities, small pulse, and low arterial blood pressure. The characteristic murmurs of mitral stenosis were much modified and the diastolic murmur may be extremely soft or entirely absent. There may be no murmurs or only an apical systolic or tricuspid systolic murmur indicative of tricuspid incompetence. Some degree of pulmonary incompetence is not uncommon. The reduced intensity or absence of the usual diastolic and presystolic murmurs of mitral stenosis is presumably due to the small volume of blood flowing through the tightly stenosed mitral valve, though it is possible that mitral calcification may have been a factor in the modification of the auscultatory signs in three of our patients (Mounsey, 1953). The electrocardiograph invariably shows the characteristic changes of right ventricular enlargement and either a P pulmonale or P mitrale may be present (Wood, 1954).

The diagnosis can usually be confirmed by finding the radiological changes of mitral stenosis and pulmonary hypertension (Wade *et al.*, 1952) with little peripheral pulmonary congestion (Fig. 2). The demonstration of a raised P.C.V. pressure at cardiac catheterization provides confirmatory evidence, but we have experienced difficulty in wedging the catheter tip in these patients, presumably owing to pulmonary arterial narrowing. The striking finding is the great increase in pulmonary vascular resistance which arises in the small muscular arteries (Davies *et al.*, 1953). This may either be the result of organic narrowing (Parker and Weiss, 1936; Larrabee *et al.*, 1949) or secondary to reversible vasoconstriction, the mode of production of which remains unknown. The increased hindrance in the region of the terminal muscular arteries undoubtedly protects the capillary bed from the output of the right ventricle, lessening the severity of symptoms due to capillary congestion. This is clearly shown in Fig. 5 which is a biopsy section from the lower lobe of the left lung of Case 6 taken during mitral valvotomy; the capillaries show surprisingly little congestion despite the tight mitral stenosis (less than 1 cm.). Wood (1952) has put forward a teleological concept of protective vasospasm but the inconstancy of this type of response renders it unlikely that this is a protective reflex mechanism. Moreover, it is of very doubtful value, for death occurs in these cases with unusual rapidity due to congestive heart failure.

Three of five patients have responded well to mitral valvotomy, two being restored to a normal life: it is still too early to assess the result in the fourth survivor. Thirty-two months after operation in Case 1, pulmonary dynamics are normal and in Case 4 the mean pulmonary artery pressure had fallen by about 50 per cent in four weeks. The remarkable clinical, radiological, and cardiographic improvement in Case 3 also must imply a considerable fall in pulmonary artery pressure. It seems probable that both vasospasm and structural changes are concerned in the maintenance of the

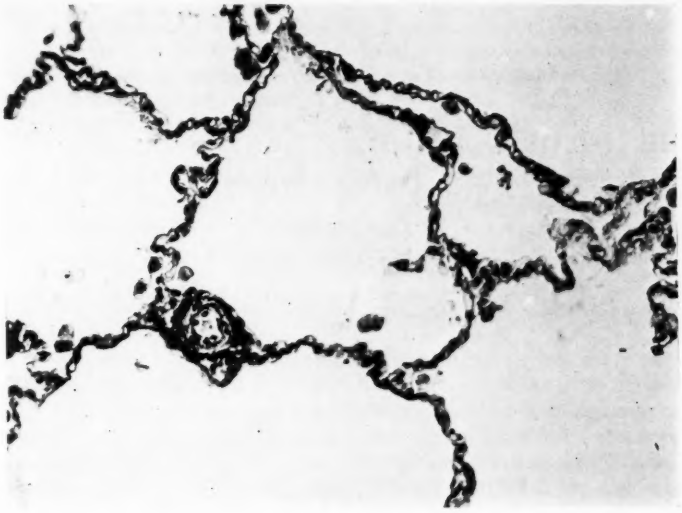


FIG. 5.—Section from lower lobe of left lung (Case 6) removed at operation, showing only slight capillary congestion in spite of severe mitral stenosis.

increased pulmonary resistance but, and this is the important fact, whatever the mechanism may be, it is potentially reversible. It is especially important, therefore, that the syndrome should be recognized for it is an urgent indication for surgery.

SUMMARY

The clinical and other features of six patients with mitral stenosis and very high pulmonary vascular resistance are reported. All had tight mitral stenosis with a valve less than 1 cm. in diameter. The natural history is short with early and intractable congestive heart failure. The symptoms are mainly those of limited cardiac output and those due to pulmonary capillary congestion may or may not be present. The physical signs of pulmonary hypertension dominate the clinical picture and the characteristic murmurs of mitral stenosis may be greatly modified or absent.

Five patients were submitted to mitral valvotomy with excellent results in three and one death; it is still too soon to assess the result in the fifth. The excellence of the operative results stresses the need for early recognition.

We are grateful to Dr. A. Morgan Jones for advice and encouragement and for permission to study patients under his care, and to Dr. J. L. Taylor and Mr. Gordon Jack for allowing us to investigate Case 6. Our thanks are due to Mr. R. C. de Meneaud for technical assistance.

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THE NATURE OF THE INCREASED PULMONARY VASCULAR RESISTANCE IN MITRAL STENOSIS

BY

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It has been known for many years that in certain cases of mitral stenosis the pulmonary arterial pressure may be disproportionately high. More recently it has been shown that this pressure, which is due to an increase in the pulmonary vascular resistance, may rise still further on effort (Bayliss *et al.*, 1950; Eliasch *et al.*, 1952). There is considerable debate as to the mechanism and significance of this increase in pulmonary vascular resistance for, as the author of a recent annotation in the *Lancet* remarked, " it is not fully understood."

In view of its theoretical and practical importance we decided to reinvestigate this problem with especial reference to the role of the autonomic nervous system. In a previous paper we reported the results of injecting adrenergic-blocking agents into the pulmonary artery in cases of mitral stenosis (Mackinnon *et al.*, 1956), concluding that they had no effect. In this paper we report the effects of hexamethonium bromide and of atropine. We find that hexamethonium will frequently lower the high resistance, but will bring forward evidence that this is an indirect action secondary to lowering the pulmonary capillary or venous pressure and independent of the autonomic system. We find that atropine has no consistent effect on pulmonary dynamics.

Material and Method

The material consisted of 18 patients suffering from mitral stenosis, all of whom had attended the Department of Cardiology at the Manchester Royal Infirmary. They were all examined in the usual manner. All were subjected to cardiac catheterization; three grains of seconal and 0·5 ml. of procaine amide were given one hour beforehand and all pressures were recorded electrically by means of a capacitance manometer. Systemic pressures were obtained through a Cournand needle placed in the brachial artery. Mean pressures were obtained by electrical damping and all pressures were referred to a point 5 cm. below the sternal notch. Blood gases were analysed on the Van Slyke-Neill manometric apparatus and expired air was collected in a Tissot spirometer and analysed on the Haldane apparatus.

Ten patients were selected because there was clinical evidence of pulmonary hypertension. At catheterization, after the basal measurements had been made, they were exercised on a bicycle-ergometer. The work varied in degree from patient to patient according to their capacity, the oxygen consumption usually varying from 250 to 400 ml./m.^{2}/min. The effort was invariably continued at a constant rate for six minutes, the output being estimated again between the fourth and sixth minutes; this was considered sufficient time for a steady state to be obtained (Eliasch *et al.*, 1952; Donald *et al.*, 1954) and this was confirmed by minute to minute measurements of pressures and pulse rate. After a period of fifteen to thirty minutes for recovery, checked by frequent pressure and pulse readings, hexamethonium bromide was injected through the cardiac catheter and the circulatory measurements repeated at rest and under identical conditions of exertion. The dose of hexamethonium was that which had been previously found, when administered intravenously, to cause a postural fall in systemic pressure of at least 25 mm. Hg, and the timing of the subsequent outputs was so arranged as to fall in the period of maximal effect. This dose varied from 8·5 to 12·5 mg. In the first seven observations the " wedge " or pulmonary capillary venous pressure (PCV) was measured only during the initial output; in the last three, it was measured during each output period. It proved impossible to exercise one patient (Case 5). One patient (Case 1) was re-catheterized four weeks after a successful mitral valvotomy.

Eight patients selected because they had auricular fibrillation and were fully under the influence of digitalis were given, after the resting measurements had been made, an injection of atropine through the catheter, the dose being from 1/120 to 1/75 of a grain. Seven of the patients were not exercised, the measurements being repeated under resting conditions; the eighth was exercised in the manner previously described before and after the administration of atropine.

Resistances were expressed in c.g.s. units and were calculated as follows.

Total Pulmonary Resistance $=(PA_m-5)\times 1332/C.O.$ in ml./sec.
Pulmonary Vascular Resistance $=(PA_m-PCV)\times 1332/C.O.$ in ml./sec.
Systemic Resistance $=BA_m\times 1332/C.O.$ in ml./sec.

where PA_m is the mean pulmonary arterial pressure, BA_m is the mean systemic pressure recorded in the brachial artery, PCV is the mean pulmonary capillary or " wedge " pressure, and C.O. is the cardiac output.

Ventricular work was calculated in terms of pressure-work only, namely, $W=PV$, where P is the mean pressure in metres of blood and V is the output in litres per hour, and was expressed in Kg. metres per hour.

Results

Hexamethonium Bromide. There was a fall in resting mean pulmonary arterial pressure in seven observations, the greatest drop being 13 mm. Hg. In one case the mean pressure rose and in three there was no appreciable change (Fig. 1A). When a fall occurred, the systolic pressure was always affected more than the diastolic. Exercise invariably caused the pulmonary artery pressures to rise; following hexamethonium this increase was less in six cases, greater in three, and unchanged in one (Fig. 1B). Changes in cardiac output were minimal and inconsistent and the pulse rate was generally unaltered.

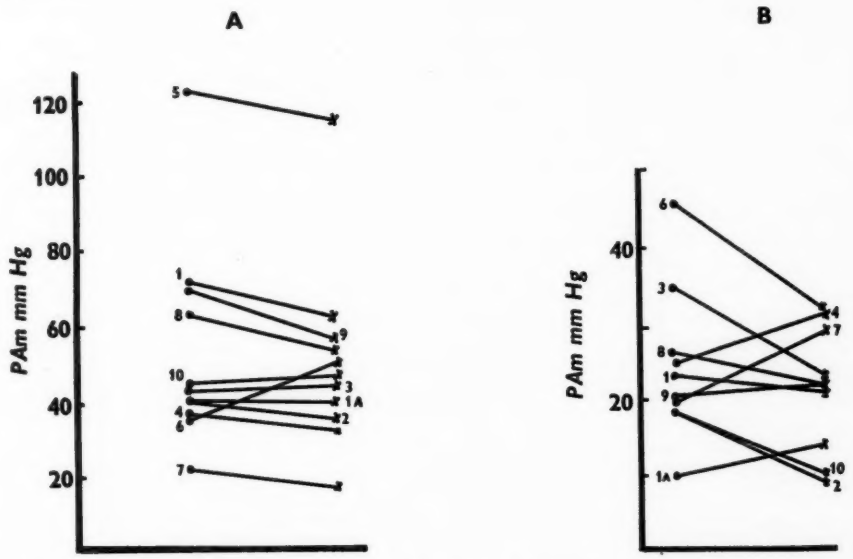

FIG. 1.—(A) The effect of hexamethonium on the resting P.A. mean pressure. (B) The change in P.A. mean pressure resulting from exercise. (● =before, and X= after hexamethonium.)

Resting total pulmonary resistance was variably affected in eight observations, there being a tendency to fall in five and to rise in three; it remained virtually unchanged in two (Fig. 2A). Expressed as a proportion of the initial basal resistance, the change was less than 10 per cent in five

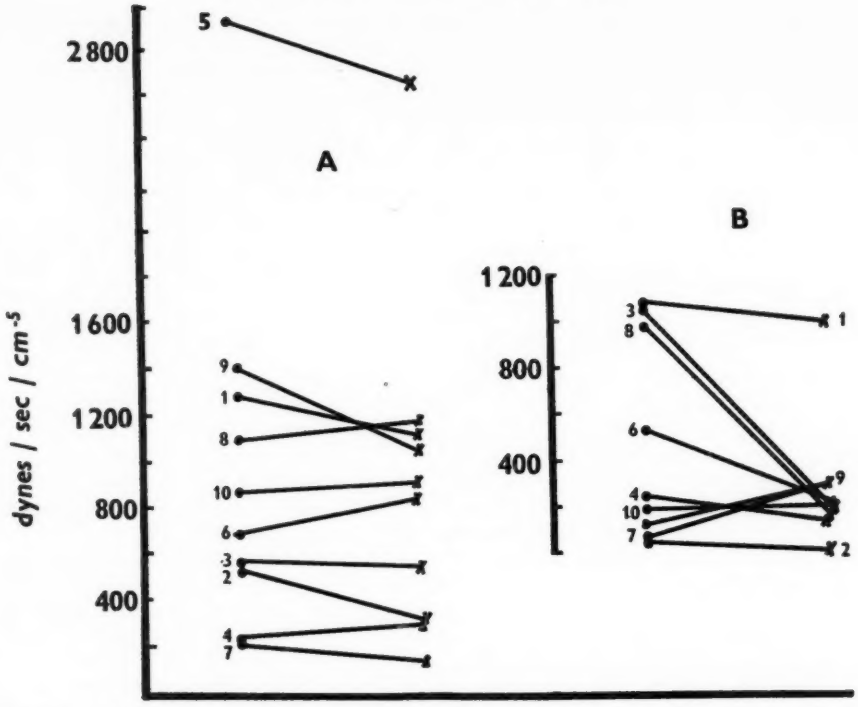

FIG. 2.—(A) The effect of hexamethonium on resting T.P.R. (B) The change in T.P.R. resulting from exercise. (● = before, and X = after hexamethonium.)

cases, fell by more than 20 per cent in three, and rose by more than 15 per cent in two (Fig. 3A). There was an increase in resistance on effort in all cases. Hexamethonium diminished the absolute extent of the increase to a variable degree in six cases; in two it was slightly augmented and in one it was unchanged (Fig. 2B). Expressed proportionately, after hexamethonium the increase on effort was altered by less than 10 per cent in four cases, diminished by more than 40 per cent in four, and increased by over 50 per cent in one (Fig. 3B). The most striking absolute and proportional " blocking " of the increased resistance on effort was achieved in Cases 3, 6, and 8, none of which had shown a fall in resting resistance. All three patients noticed subjective improvement on exercising after hexamethonium. There is, therefore, no apparent relation between the effects of hexamethonium on the resting resistance and the extent of the increase in resistance occurring on effort (c.f. Fig. 2A and B and 3A and B).

There was a fall in the resting *PCV* pressure after hexamethonium in two of three cases (8 and 9), while in the third there was a slight rise (10) (Fig. 4). In Cases 8 and 9 the extent to which the *PCV* rose on effort was also diminished; in Case 10 there was no change. In Fig. 4 the pulmonary vascular resistance at rest and on effort before and after hexamethonium is related to the *PCV* pressure; there is a direct relation, both in individual cases and in the three cases taken together ($r = +0{\cdot}59 : I/\sqrt{N-I} = 0{\cdot}61$).

The work performed by each ventricle varied considerably from case to case. With the exception of Case 1, effort always caused a rise in right ventricular work; after hexamethonium the degree of this rise was increased in six cases, diminished in one, and unchanged in two. The left ventricular work pattern was rather different. In three cases (1, 3, and 8) effort caused a fall in the work done and, in two of them (3 and 8), this was converted into a rise after hexamethonium. These

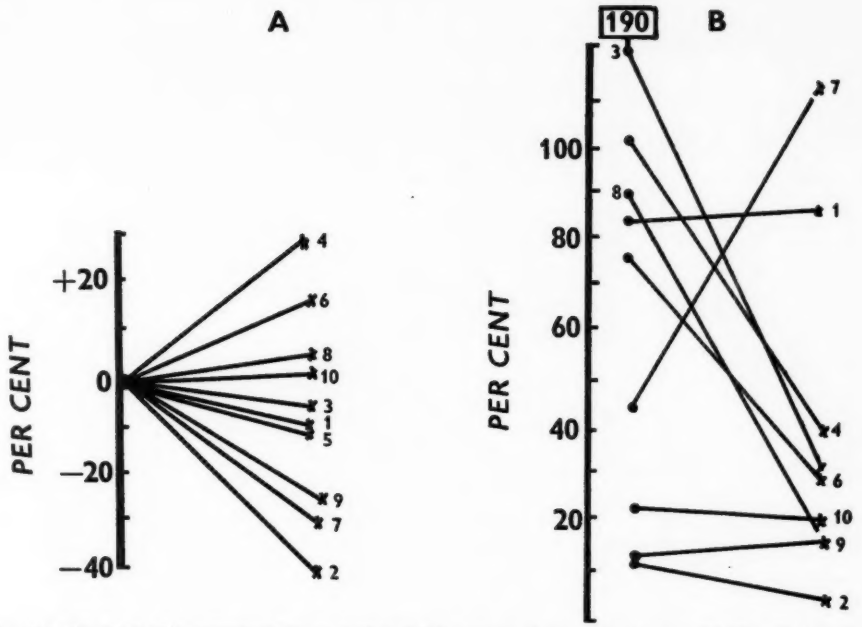

FIG. 3.—(A) The effect of hexamethonium on resting T.P.R. expressed as a percentage. (B) The effect on the rise in T.P.R. on effort expressed as a percentage of the initial T.P.R. (● = before, and X = after hexamethonium.)

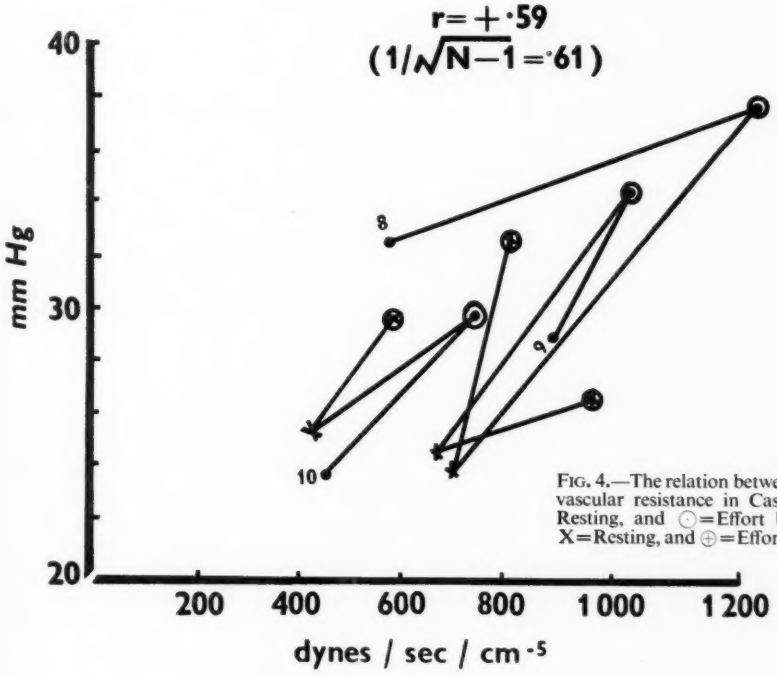

FIG. 4.—The relation between *PCV* and pulmonary vascular resistance in Cases 8, 9, and 10. (● = Resting, and ⊖ = Effort before hexamethonium. X = Resting, and ⊕ = Effort after hexamethonium.)

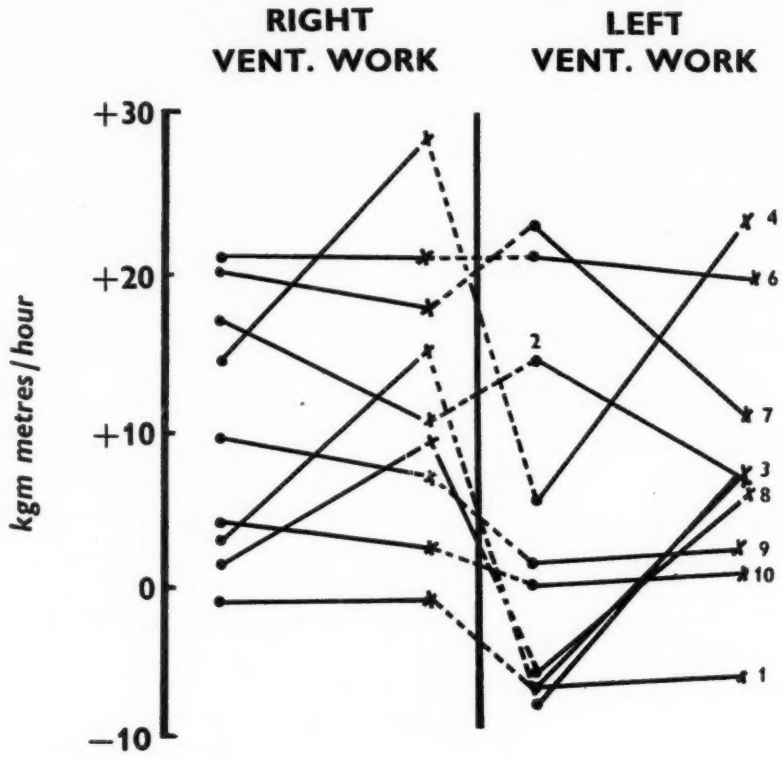

FIG. 5.—The changes in right and left ventricular work occurring on effort before (closed circles) and after (crosses) hexamethonium. The interrupted lines connect the same patient.

were two of the three cases in which hexamethonium had the most striking " blocking " effect on rise in pulmonary hindrance on effort. In all other cases left ventricular work increased on effort to an extent that was unchanged by hexamethonium in four cases, slightly diminished in two, and increased in one. These results are summarized in Fig. 5.

Case 1 was recatheterized four weeks after successful mitral valvotomy. Although hexamethonium, prior to operation, had produced only a small fall in total pulmonary resistance from 1310 to 1150 units, it subsequently fell to 500 units. Moreover, the increase in resistance occurring on effort, unaffected before operation by hexamethonium, was decreased from over 1000 to 55 units (Fig. 6). The resting *PCV* pressure was reduced from 25 to 7 mm. Hg. Owing to a technical fault the resting outputs after operation were unreliable, but comparison may reasonably be made between the effort patterns under the influence of identical doses of hexamethonium.

Atropine. There was no consistent effect either upon pressures or upon resistances. The mean P.A. pressure rose appreciably in Cases 12 and 13; the *PCV* rose from 27 to 31 mm. Hg in Case 12 but was not obtained in Case 13. In both there was an increase in the pulse rate of over 20 beats a minute. In Case 16 total pulmonary resistance fell by 200 units but in the remainder there was no significant change. Changes in cardiac output were small and inconsistent. Only one case (18) was exercised before and after atropine; neither the resistance nor the output was appreciably affected. The pulse rate on effort was 120 before and 140 after the drug.

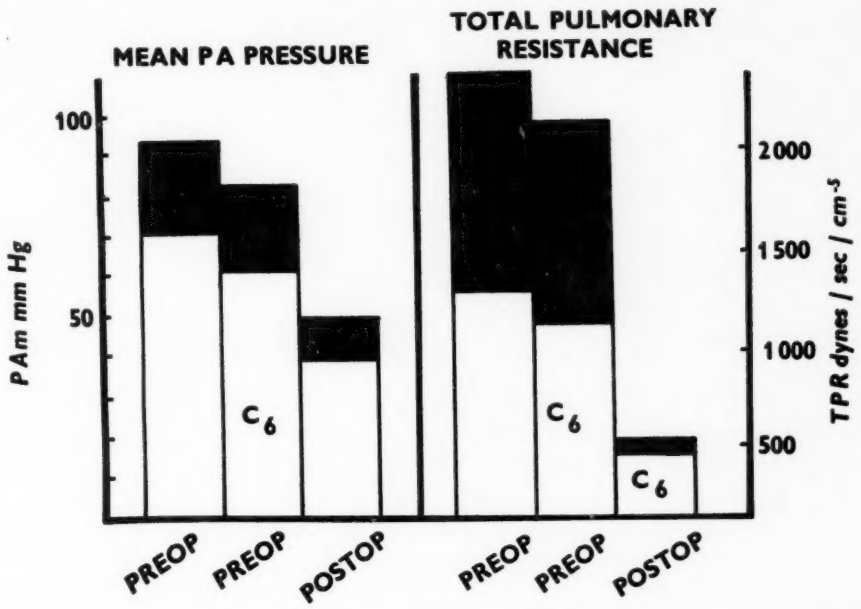

FIG. 6.—The effect of hexamethonium on P.A. mean pressure and T.P.R. in Case 1, together with the finding one month after successful valvotomy. White=resting. Black= increment on effort. C_6=hexamethonium.

DISCUSSION

Hexamethonium caused a fall in resting mean pulmonary arterial pressure in the majority of our cases and this harmonizes with the findings of Davies *et al.* (1954), Storstein and Tveten (1954), Halmagyi *et al.* (1953) and Scott *et al.* (1955). In terms of resistance, however, the change is trivial in five cases, such pressure changes as occur being ascribable to alteration in cardiac output. In two others the resting resistance actually increased, so that there was a significant fall in only three of the ten cases. Unfortunately Davies *et al.* did not calculate the pulmonary resistance, while Halmagyi *et al.* used the pulmonary arterial systolic pressure in calculating resistance and we have noted that the systolic pressure was invariably affected to a greater extent than the mean. With the exception of Storstein and Tveten, all these authors interpreted their results as evidence that the autonomic nervous system participated in maintaining the high pressure. A similar conclusion was reached by Meriel *et al.* (1953) on the grounds that hydergine, an adrenergic-blocking agent, would also reduce the pulmonary hypertension of a variety of clinical conditions. Comparison of the effect of hexamethonium upon resting and exertional dynamics throws some doubt on the validity of this conclusion, for the greatest effect on the two patterns was not necessarily seen in the same case; it is reasonable to anticipate that this would have been so if the resistance, in both instances, was a matter of simple sympathetic overactivity (Fig. 1, 2, and 3). There are certain other objections to this concept of sympathetic overactivity: no physiological mechanism is known involving sympathetic control of pulmonary vessels, adrenalin does not cause pulmonary hypertension in normal subjects (Witham and Fleming, 1951), and we have been unable to confirm that hydergine or priscol (2-benzyl-2-imidazoline) will lower the pulmonary resistance in mitral stenosis (Mackinnon *et al.*, 1956). It may be argued that, whereas the rise in hindrance on effort is vasoconstrictive, a high resting hindrance unaffected by hexamethonium means a degree of irreversible structural change. This concept of combined structural and vasospastic narrowing has been put

forward to account for the frequent failure of both ganglion-blocking and adrenergic-blocking agents, to lower raised pulmonary pressures (Meriel *et al.*, 1953; Scott *et al.*, 1955). It is difficult to explain, on this basis, the paradoxical findings in Cases 8, in which resting pulmonary vascular resistance is not affected but the vasoconstriction response to effort is largely prevented, and 9, in which resting resistance falls but the vasoconstriction response still occurs. Scott *et al.* have even gone so far as to suggest that the response to a ganglion-blocking agent, in their case tetraethyl-ammonium chloride (T.E.A.C.), will serve to differentiate cases in which a good or poor result may be expected from mitral valvotomy. In our Case 1 hexamethonium had singularly little effect on the resting or exercise patterns but, within four weeks of operation, pulmonary hindrance had fallen to one-fifth of its former value and there was almost no rise on effort (Fig. 6). Werko, *et al.* (1952) have also reported large falls in pulmonary vascular resistance in cases of mitral stenosis within a month of operation, providing that the *PCV* pressure was satisfactorily reduced. Clearly the initial high resistance in our case must have been largely due to vasocontraction and not to irreversible structural change. Equally clearly, ganglion-blocking drugs must not be used to select cases for surgery.

It has long been known that there is a direct relation between the *PCV* pressure and the pulmonary vascular resistance, and that, although a high *PCV* may occur with a normal resistance, a high resistance always implies a high *PCV* (Eliasch *et al.*, 1952; Wade, 1952; and Wood, 1954). In those of our cases in which it was measured on each occasion, (8, 9, and 10) there was a direct relation between *PCV* and resistance, and hexamethonium did not reduce the hindrance without a fall in *PCV*. An indirect action through an effect on *PCV* pressure would explain the differing effect on resistance at rest and on effort, the diminution in respiratory distress experienced by Cases 3 and 8 when exercising after hexamethonium and also the observation of Davies *et al.*, otherwise inexplicable, that pulmonary œdema was relieved by hexamethonium in two of their cases. Such an indirect action would permit explanation of the failure of hexamethonium to reduce the resistance in Case 1, despite a rapid fall following successful valvotomy. Only one other study of the effects of hexamethonium in which *PCV* pressures were recorded has been reported (Scott *et al.*, 1955): it fell in only one of three cases in which the pulmonary vascular resistance was reduced. Their results are not entirely comparable with ours, for they used T.E.A.C., in doses so large that there were substantial falls in the systemic pressure with the patients lying down. There may thus have been considerable pooling of blood in the systemic circuit. We suggest that the concept that changes in pulmonary vascular resistance following hexamethonium are linked to, and dependent on, changes in *PCV* pressure is entirely consonant with our findings and we consider it to be the most reasonable hypothesis. It would also accord with the observation made by Wade and Ball (1956) that, in unexplained pulmonary hypertension with normal *PCV* pressures, hexamethonium is without effect.

There are several ways in which hexamethonium might affect the *PCV* pressure. It has been shown that the lung blood volume is directly related to the capillary pressure (Kopelman and Lee, 1951; Wade *et al.*, 1952) and, on exercise, both pressure and volume tend to rise (Wade, 1952) Storstein and Tveten, in a careful analysis, concluded that the effects of hexamethonium could be explained by reduction in pulmonary blood volume due to pooling of blood in the systemic circuit. We do not know the extent of the volume changes in our cases, but we have tried to minimize them by using a dose known to be effective but too small to cause a fall in systemic pressure with the patient lying down. It must be admitted, however, that volume changes may play a part in altering pressure/flow relations in the lungs in our cases, and must certainly be a factor when such large doses of hexamethonium are given as by Davies *et al.* and Scott *et al.* Changes in cardiac output and pulse rate may be discounted, for they were minimal and inconsistent. The effect on tonus of the pulmonary veins and left atrium is unknown; clearly, any appreciable decrease in tone would, by redistributing blood within the lungs, profoundly affect pressure/flow relations in the capillary bed. Another possible factor is a change in left ventricular filling pressure. In Cases 3 and 8, there was, initially, a fall in left ventricular work on effort. Although hexamethonium did not affect resting dynamics,

a corresponding amount of exercise now produced a striking rise in left ventricular work (Fig. 5). A similar change was seen in Case 1 following operation. This may be entirely due to diminished resistance to blood flow through the lungs and, in consequence, improved left ventricular filling, but it is also possible that left ventricular failure, with a rise in left ventricular filling pressure, occurred during the first period of effort. Direct catheterization of the left ventricle through a needle inserted into the left auricle has shown that, in pure mitral stenosis, the filling pressure of the left ventricle at rest may be as high as 11 mm. Hg. (Fox *et al.*, 1956). It is probable that more than one of these factors is concerned but our data do not enable us to distinguish between them.

The mechanism whereby changes in *PCV* or pulmonary venous pressure—and we are unable to distinguish between them—affects vascular hindrance in some cases but not in others remains obscure. When the resistance rises it must be due, partly or wholly, to active contraction of the muscular pulmonary arteries, but we have brought forward evidence that the sympathetic system is not concerned. There must be, however, in the normal lung, some mechanism for maintaining a higher vascular tone in the dependent parts of the lung, for, in the erect position, there is a 20 mm. Hg. pressure-gradient between apex and base. It is also a not uncommon post-mortem observation that in cases of mitral stenosis with high resistance, there are scattered areas of pallor usually confined to the lower lobes (Campbell, 1956). An attractive and reasonably satisfying hypothesis would be a local veno-arterial or capillary-arterial reflex, similar to that reported by Haddy and Gilbert (1956) to occur in the limb vessels of the dog. These workers found that raising the pressure in a particular vein caused a variable, and often disproportionate, rise in pressure in the corresponding arteriole; the reflex persisted after nerve block and did not necessitate an intact sympathetic supply. A somewhat similar mechanism had been noted in the limbs of rabbits by Girling (1952). Such a hypothesis would harmonize with the belief that anoxia, one of the few stimuli that will cause vasoconstriction in the normal lung, also acts through a local reflex, for the effect is known to be independent of autonomic innervation (Liljestrand, 1948; Nisell, 1951*a* and *b*).

The slight increase in total resistance noted in four of eight cases following atropine may be ascribed to the induced tachycardia with consequent reduction in diastole. We had hoped that, by selecting cases of auricular fibrillation fully under the influence of digitalis, we would avoid the complication of severe tachycardia, but this was not the case. Kaunitz and Andersen (1954) suggested that, in the dog, vasoconstrictor fibres to the lungs might be carried in the parasympathetic. nerves, but our results yield no confirmation that this is so in man.

Summary and Conclusions

Hexamethonium bromide was injected into the pulmonary artery in ten cases of mitral stenosis with clinical evidence of pulmonary hypertension. The effects produced on circulatory dynamics both at rest and on effort are reported.

Hexamethonium often lowered the pulmonary vascular resistance and this occurred in association with a reduction in pulmonary capillary venous pressure.

It is suggested that hexamethonium acts by lowering the pulmonary capillary venous or pulmonary venous pressure and that this causes a fall in pulmonary vascular resistance by means of a local reflex which is not under autonomic control.

Atropine was administered intravenously to eight subjects with severe mitral stenosis and auricular fibrillation fully under the influence of digitalis. It was not found to have any consistent effect.

We thank Professor Colin Campbell for his help regarding certain pathological features of the lungs in mitral stenosis, Dr. A. Morgan Jones for his encouragement and for permission to examine patients under his care, and Mr. R. C. de Meneaud for technical assistance. Finally, we thank our patients for their willingness to co-operate in long and arduous observations.

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A CLINICAL METHOD OF STUDYING THE ELASTICITY OF LARGE ARTERIES

BY

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Studies of the physical characteristics of large arteries (Roy, 1880; Bramwell, 1924; Hallock and Benson 1937) have shown that the aorta is more elastic in the young than in the elderly. As age advances the great vessels dilate while their distensibility diminishes and the range of pressure over which the wall is approximately elastic is reduced. These changes are the result of the tension in the arterial wall being thrown on to the collagen fibres as the elastic tissue deteriorates. Clinical studies of arterial elasticity have been made by Bramwell and Hill (1922). Their method was based upon the velocity of transmission of the pulse wave, which is determined by the physical properties of the vessel wall. The pulse wave velocity was found to increase with age (Bramwell *et. al.*, 1923 *b*) and with the elevation of pressure across the wall of the artery (Bramwell *et. al.*, 1923 *a* and *c*). This work contributed much to the understanding of the effect of age upon the arterial tree; it confirmed, *in vivo*, the arterial changes, described earlier, in excised strips of aorta, and showed that loss of elasticity was not confined to the aorta and its immediate branches, but spread to the smaller and more muscular vessels, for example, from the brachial to the radial arteries. The consequence of this is seen in the well-known increase of pulse pressure with age (Master *et al.*, 1943; Hamilton *et al.*, 1954; Miall and Oldham, 1955). Unfortunately, the elasticity of the large arteries cannot be assessed by pulse pressure measurements alone since the latter are affected by other variables such as stroke volume, the force and duration of ventricular ejection, the peripheral resistance, and the volume of the great vessels.

The test to be described attempts to establish clinically whether the vessels forming the main arterial reservoir are mainly elastic or whether the tension is being thrown on to the inelastic collagen. The differentiation depends upon changes in pulse pressure occurring in vessels when the level of diastolic pressure is reduced with little change in stroke volume. From the data obtained by Roy (1880), Hallock and Benson (1937), and Remington *et al.* (1948) it is possible to predict that in young, more or less elastic arteries little change in pulse pressure would occur as the blood pressure was reduced without changing stroke volume, whereas in elderly, inelastic arteries progressive diminution in pulse pressure would be seen as the diastolic pressure fell. This theoretical basis of the test will be considered in greater detail later.

The method requires that the diastolic pressure should be reduced without significantly affecting the volume of blood ejected by the heart at each beat. Observation of the effect of nitroglycerine on the blood pressure in animal experiments suggested that this might be achieved for a limited number of heart beats, immediately after the inhalation of amyl nitrite, when an appreciable interval occurs during which the diastolic pressure falls but the heart rate is unchanged (Conway, 1955). If it were assumed that the stroke volume was not significantly changed at this early stage, then pulse pressure measurements could be made from beat to beat against a falling level of diastolic pressure and this would indicate whether the arteries were elastic or inelastic. The assumptions involved in the test will be considered later, but it so happened that tracings of the effect of amyl

nitrite in young normal subjects and patients with hypertension, taken for another purpose, were available for study and a survey of these was sufficiently encouraging to justify pursuing the matter further. Additional clinical material was therefore obtained to investigate the reliability of the test.

Material and Method

Fifteen normal volunteers, medical students, and thirty-seven patients, admitted to hospital with hypertension, have been studied. Patients with clinical evidence of heart failure were excluded. The test was conducted with the subjects lying comfortably on a couch while the blood pressure was measured by a condenser manometer connected by a short length of polythene tubing (approx. 20 cm.) to a needle (SWG 25) lodged in the brachial artery, after infiltration of the skin and superficial fascia with procaine or lignocaine. The region of anæsthesia was not extended to include the artery. At frequent intervals the needle in the brachial artery was flushed through with heparinized saline to ensure accurate transmission of the pulse pressure. The condenser manometer was also checked repeatedly against known static pressures. The natural frequency of the system was approximately 20 cycles per second. The electrocardiogram and the respiration were also recorded in many instances. Records were made with ink-writing oscillographs or photographically with mirror galvomanometers. Care was taken to compare the pulse pressures in equivalent heart beats before and at the onset of the depressor effect of amyl nitrite, particular attention being given to the duration of the cardiac cycle and the phase of respiration.

After recording the initial blood pressure tracing, a crushed phial or a container of amyl nitrite was held under the subject's nose for one or two breaths and then withdrawn. The subject was clearly instructed not to " sniff " the vapour, since this would affect the venous return to the heart. In 22 subjects (9 normal and 14 with hypertension) the test was repeated more than once, and in 4 subjects an opportunity was available to repeat the test on another occasion. It was also possible to repeat the test after the administration of hexamethonium (20–30 mg. intravenously) in 7 normal subjects and 11 patients with hypertension.

Results

The response to the inhalation of amyl nitrite, like that to an injection of nitroglycerine, may be divided into three physiological phases. The blood pressure tracing in the first phase shows a falling diastolic pressure for a limited number of heart beats without change in heart rate. The effect of amyl nitrite is seen therefore without the interference of the regulatory reflexes from the aorta and carotid sinus. After a certain fall in blood pressure the reflexes come into play and the second phase begins with tachycardia and vaso-constriction which limits the fall in pressure and rapidly restores it to normal. The third phase then follows during which the pressure is maintained at its initial level by the regulatory reflexes in spite of the continued depressor effect of the drug (Conway, 1955).

Amyl nitrite was given by inhalation in preference to intravenous injections in order to minimize the effect upon the pulmonary circulation and hence upon the filling of the left ventricle. The inhalation itself unfortunately had its own disadvantages, since it sometimes raised the blood pressure and affected the heart rate in some nervous patients. This made the tracings difficult to analyse since pulse pressure measurements preceding the inhalation could not be used for comparison with those occurring with the falling blood pressure. In these instances it was nevertheless possible to measure the pulse pressure against a declining level of diastolic pressure for an adequate number of beats in which the heart rate was steady.

The first phase of the effect of amyl nitrite has been utilized for the test of arterial elasticity since the effect of a falling diastolic pressure on the pulse pressure was seen without change in heart rate, and it was assumed that little change in stroke volume occurred at this stage. The onset of reflex tachycardia was determined very accurately even in the presence of sinus arrhythmia because the change was progressive, reaching a maximum at the time of, or just after, maximal

depression of blood pressure. One of the main difficulties of the test was that the first phase was sometimes very short and the reduction of diastolic blood pressure small. In the normal and hypertensive subjects 84 tests were performed without the use of hexamethonium, and in these tests eight heart beats was the average number available for study, while the average reduction in diastolic pressure was 15 mm. Hg. Fig. 1 shows the tracing obtained in a test in a normal subject

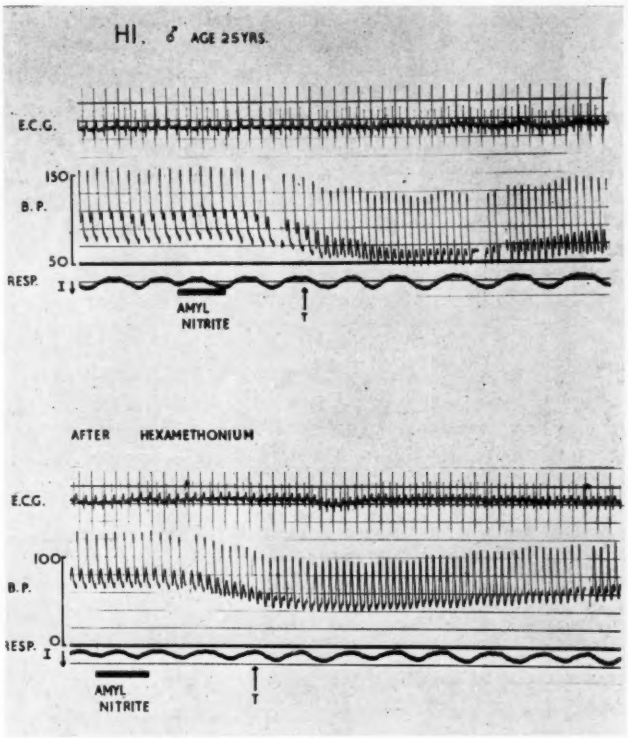

FIG. 1.—The effect of the inhalation of amyl nitrite on the blood pressure in a normal subject, before and after hexamethonium. Note gaps in the pressure tracing occur when the needle is being washed through with heparinized saline. A time-tracing is run with the electrocardiogram at 1/sec. T indicates the point at which tachycardia appeared.

in which the number of beats was limited to five and it is shown that this difficulty could be overcome by partially blocking ganglionic transmission by an injection of hexamethonium dibromide (20 mg. I.V.). This diminished the vagal restraint upon the heart and delayed the onset of reflex response to the falling blood pressure. In 17 subjects in whom the test was repeated after hexamethonium, the average number of heart bests available for study was increased to 12, with a greater average fall of the diastolic pressure to 18 mm. Hg. Since the efficiency of the regulatory reflexes was impaired by hexamethonium it seemed wise to reduce the concentration of amyl nitrite or the duration of the inhalation. The increase in the depressor response was therefore not as great as it might have been. The combination of the two drugs produced no ill-effects. Hexamethonium was particularly useful in another way since it practically abolished changes in blood

pressure and heart rate produced by the act of inhaling the drug and it also abolished sinus arrhythmia.

To assess changes in elasticity of the large arteries the change in pulse pressure after amyl nitrite was compared, for each heart beat, with the reduction in diastolic pressure, and the relationship between them expressed as a ratio $\frac{\text{Change in pulse pressure}}{\text{Change in diastolic B.P.}}$. In order to obtain a single figure for each test, the average was taken of this ratio in the three consecutive beats in which the reduction of diastolic pressure was greatest and before tachycardia occurred; the change in pulse pressure was then expressed as a percentage of the change in diastolic pressure.

Studies of normal subjects have been confined, for the present, to the young, since it would be unlikely that they would show evidence of deterioration in elastic tissue. In age, the 15 normal subjects ranged from 17 to 32 years and in the 28 tests performed without hexamethonium, the reduction in pulse pressure with a falling diastolic pressure was very small, the average being 16 per cent of the reduction in diastolic pressure. On repetition of the test after hexamethonium in 7 subjects, the change in pulse pressure was again quite small—18 per cent. of the reduction in diastolic pressure.

All the patients studied had been admitted to hospital with hypertension but, in a few, the blood pressure at the time of the test had fallen to normal. Since the present study is concerned primarily with the presentation of the method, the findings in these patients have not been grouped separately. The 37 patients, on whom 56 tests were performed without hexamethonium showed two types of response (Fig. 2) as below.

Group I (*15 patients*). These gave results similar to the normals; the reduction in diastolic pressure had little effect on pulse pressure, the average reduction being 31 per cent of the change in diastolic pressure in this group. In 5 patients in whom the test was repeated after hexamethonium, the change in the pulse pressure remained at 25 per cent of the fall in diastolic pressure. This group has been called the "elastic hypertension" and the limits in this group were determined by the findings in tests on young normal subjects.

Group II (*22 patients*). In these, the response was entirely different. The reduction in diastolic pressure was accompanied by a conspicuous drop in pulse pressure. It was reduced by an average of 97 per cent of the change in diastolic pressure. In the 6 patients of this group in whom the test was performed after hexamethonium, the pattern of the response was unchanged, with a reduction of pulse pressure averaging 110 per cent of the fall in diastolic pressure. We have called this group the "inelastic hypertension".

When those with hypertension have been grouped as above according to their responses in the test it can be seen that patients in the inelastic Group II are on average 11 years older, and have a higher pulse pressure than those in the elastic Group I, showing that in general the separation achieved by the test agrees with clinical findings (Table). The average diastolic pressure in the inelastic group was little raised; this was because 7 out of 22 patients in this group had arteriosclerotic hypertension, with high systolic pressure but approximately normal diastolic pressure. There were no patients with arteriosclerotic hypertension among those in the "elastic" group. A clinical study of patients with hypertension will be given when further data have been accumulated, but it is of interest to note here that there were three patients in the inelastic group who were under 50 years of age: two had arterial disease, one angina and the other arteriosclerosis obliterans with gangrene of the right great toe, and the third had a history of renal tuberculosis, diagnosed 14 years earlier.

An estimate of the reliability of the test was obtained by making repeated observations on 23 subjects, 9 controls and 14 with hypertension. In four of the patients, these repetitions were performed on a separate occasion. The relationship between pulse pressure and diastolic pressure was little changed. The first test in all these subjects showed that the average fall of pulse pressure was 64 per cent of the reduction in diastolic pressure while for the subsequent tests on the same subjects the corresponding figure was 74 per cent.

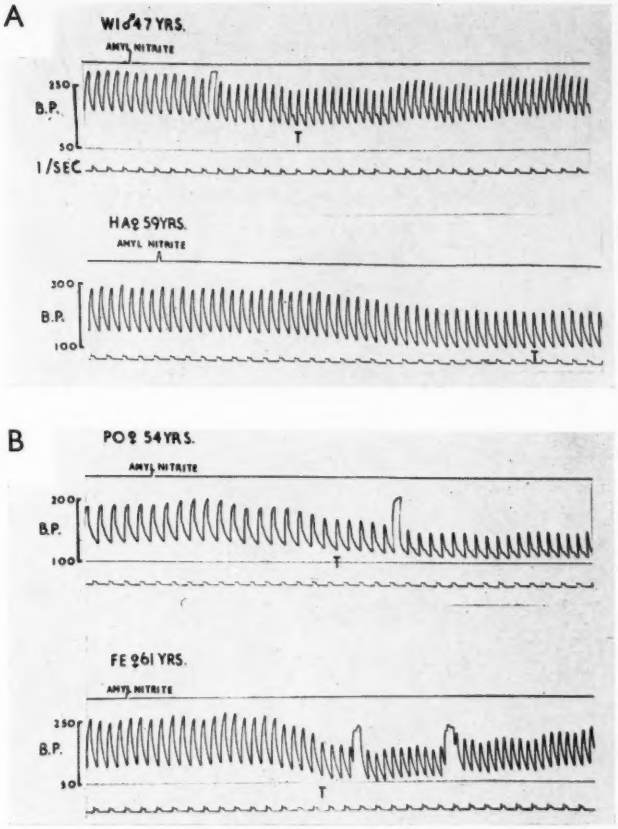

FIG. 2.—The effect of the inhalation of amyl nitrite on the blood pressure in four patients with hypertension. (A) From the group with "elastic hypertension." (B) From those with "inelastic hypertension"

CLINICAL DATA OF NORMAL AND HYPERTENSIVE SUBJECTS, AND THE EFFECT OF AMYL NITRITE ON THE PULSE PRESSURE

Subjects	Average age (years)	Average initial blood pressure			Average rate (beats/min.)	Average change in pulse pressure (as percentage of the reduction in diastolic pressure)
		Sys. mm. Hg	Dias. mm. Hg	Pulse P. mm. Hg		
Normal (15)	24	124	71	53	78	16% (S.D. 18·8)
Hypertensive "elastic" (15)	46 (S.D. 9·6)	219	131	88 (S.D. 23)	87	31% (S.D. 19·7)
Hypertensive "inelastic" (22)	57 (S.D. 7·0)	216	105	112 (S.D. 18·6)	82	97% (S.D. 24·7)

Note. Between the two groups of hypertensive patients significant differences exist in age ($t=5·2$, $P<0·001$), initial pulse pressure ($t=3·4$, $P<0·01$) and in the change in pulse pressure after amyl nitrite ($t=8·7$, $P<0·001$).

Discussion

The feasibility of this new method of determining the state of the elastic tissue of the great arteries depends upon the possibility of reducing diastolic pressure without significantly affecting stroke volume. Before changes in pulse pressure after amyl nitrite can be taken to indicate changes in the elasticity of the larger arteries, certain assumptions have to be made, the most important of which are as follows.

(1) There should not be a significant reduction in venous return to the left ventricle.

(2) The reduction in blood pressure should not lead to a significant increase in the discharge from the left ventricle.

(3) Amyl nitrite itself should not produce significant changes in the elasticity of the large vessels.

Hæmodynamic studies of the effect of nitrites in the first phase have not been performed since they would require methods that could follow changes from one heart beat to the next. The reduction in venous return after nitrites (Weiss *et al.*, 1937; Wilkins *et al.*, 1937) occurs in the second or third phase of their effect when the moderator reflexes are acting most strongly. Animal experiments have shown (Conway, 1955) that maximal depression of blood pressure can be produced by nitroglycerine with little change in pulse pressure if the regulatory reflexes are blocked by hexamethonium, indicating that nitrites do not of themselves diminish venous return and consequently cardiac output. This finding has been confirmed in further unpublished animal experiments in which the effect of nitrites has been studied with a cardiometer. With the reduction of pressure, the stroke volume was not reduced but, on the contrary, increased slightly. The possibility therefore exists that in some patients the test might be invalidated because the stroke volume increased and thus obscured a reduction in pulse pressure. It was thought, however, that in the absence of heart failure this complication would be insignificant, since changes in pulse pressure were measured from one beat to the next and the reduction in diastolic pressure between beats was small, varying from 1 to 4 mm. Hg. On theoretical grounds, therefore, and after some preliminary experiments it was thought that none of the factors enumerated would change sufficiently to affect the test.

The theoretical background of the test requires separate consideration since it depends upon an analysis of the physical properties of arteries. A strip of perfectly elastic material would show a linear/length relationship, as required by Hooke's law, and as shown schematically in Fig. 3 (solid line). Derivation of the pressure/volume relationship of a vessel made of this material is unexpectedly complicated, since both pressure and volume are a function of the radius of the vessel, but it can be shown mathematically that the volume will rise steeply with equal increments of pressure, as in Fig. 4 (solid line). Arteries, like other biological tissues, are never perfectly elastic (Roy, 1880) but in the arteries of young animals there is a tendency to obey Hooke's law at lower ranges of pressure, but this is lost as the pressure is raised above the normal level. This is shown graphically by the dotted lines in the illustrations, where the sigmoid character of the pressure volume curve is characteristic of the findings obtained in the young by Roy (1880), Hallock and Benson (1937), and Remington *et al.* (1948). The failure to obey Hooke's law is progressively greater as the pressure is raised, owing to the fact that the tension is thrown on to the collagen fibres, particularly in the adventitia, which are inelastic. From the point of view of the present test, however, it will be seen that for elastic arteries over a wide range of pressure equal increments of volume would give approximately equal changes in pressure. In the young, and in normally elastic arteries, there should be little change in pulse pressure as the diastolic pressure is reduced providing the stroke volume remained unchanged. With ageing, the level of pressure at which the artery becomes inelastic is greatly reduced, and eventually it is seen that the artery becomes inelastic even at very low pressures and the pressure/volume curve differs greatly from that obtained in the young (Fig. 5). Equal increments of volume result in greater and greater increases in pressure. In the elderly, therefore, if the stroke volume is held constant and the diastolic pressure is reduced, the pulse pressure will also be reduced (Fig. 5).

The results of the test with amyl nitrite in normal subjects showed a small reduction in pulse

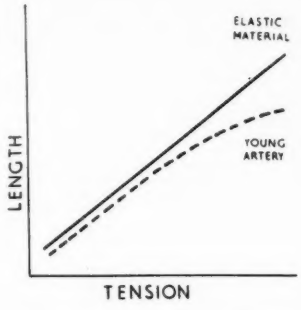

FIG. 3.—Tension/length diagram of a strip of elastic material (solid line) and a strip of artery from a young person (dotted line).

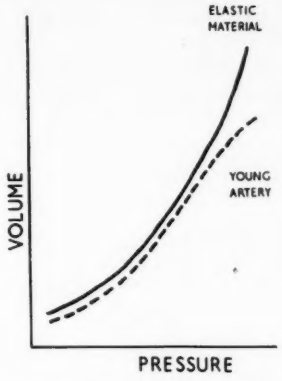

FIG. 4.—The conversion of curves in Fig. 3 for an elastic material and a young artery into a pressure/volume diagram.

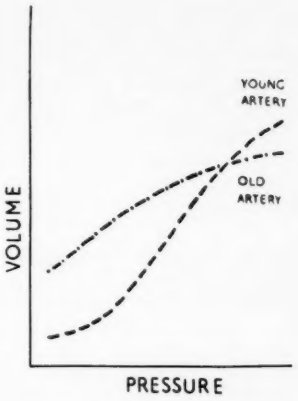

FIG. 5.—The pressure/volume relationship of arteries of young and old subjects.

pressure with the falling diastolic pressure and if the assumptions are valid, this indicates that their arteries were moderately elastic. This was also true of the " elastic " hypertensive group and the clinical findings in this group agreed with the findings in the test. The clear reduction in pulse pressure with the falling diastolic pressure in the remainder of those with hypertension indicated that their arteries were inelastic and this was confirmed in a general way by their greater age and greater initial pulse pressure, and this group included cases of arteriosclerotic hypertension. In most patients, the clinical features alone would not have been sufficient to assign them to one group or to another. No attempt has been made to assess the extent of the degenerative change in the arterial reservoir, and the limits of the elastic group have been determined by the findings in the normal subjects. More precise classification should be possible when we have applied the method more extensively. For the present, the term " inelastic " has been used in preference to " sclerotic " since it was appreciated that some cases might appear to be inelastic, not because of fibrous changes in their arteries but because the diastolic pressure might be high enough to throw considerable tension on the inelastic collagen material of the adventitia.

Although this test has been worked out on patients with hypertension among whom it has been useful in the separation of two distinct types, it is hoped that in providing a clinical method of assessing the process of ageing in arteries it may be equally useful in other arterial diseases. It may thus be possible to clarify the association between the elevation of blood pressure with age and loss of elasticity. It also offers an opportunity of studying the elastic state of the large arteries in coronary and cerebral arterial diseases, and of determining whether an association exists between the atheromatous arterial diseases and loss of elasticity.

SUMMARY

Immediately after the inhalation of amyl nitrite, the blood pressure may be seen to fall for a certain number of heart beats without change in heart rate. If it can be assumed that there is no significant change in stroke volume at this time, changes in pulse pressure may be used to indicate the elasticity of the large arteries.

The feasibility of using a test based upon this principle has been studied in 15 normal young subjects and in 37 patients with hypertension. In the young, as was predicted from theoretical

considerations, the reduction in diastolic pressure was accompanied by little change in pulse pressure, the average being 16 per cent of the fall in diastolic pressure. In the group of patients with hypertension two types of response were seen. In one group the average reduction in pulse pressure was quite small, 30 per cent of the reduction in diastolic pressure, while in the other it almost equalled the reduction in diastolic pressure, an average of 97 per cent. The former has been called the "elastic" and the latter the "inelastic" hypertensive group. The clinical data were in general agreement with this classification in that the patients of the inelastic group were significantly older than those in the elastic group and their initial pulse pressure was also significantly greater.

We should like to acknowledge the help and co-operation of the students who volunteered for these tests, the physicians of Charing Cross Hospital who gave access to their cases, and of Miss Anne Smith, cardiographic technician, and Mr. W. Penn for their conscientious technical assistance.

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THE COURSE AND PROGNOSIS OF COARCTATION OF THE AORTA

BY

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A beautiful description of the collateral circulation was given by Bramwell and Morgan Jones (1941), and Bramwell (1947) discussed the clinical features and prognosis.

The prognosis of patients with coarctation of the aorta is judged mainly from studies of those who have died in hospital, for no large series seemed to have been followed clinically for many years. To advise a patient wisely whether he should undergo operation demands a knowledge of the prognosis, and this will become more difficult to acquire as increasing numbers take advantage of the operation that was shown to be possible by Crafoord and Nylin in 1945. This paper is based on a study of 130 patients, mainly in an attempt to assess the prognosis, about which we have become less satisfied, for an absence of significant symptoms gives no certainty of continuing good health, even for the next few years.

Incidence. Coarctation occurs in from one in a thousand (Fawcett, 1905; Blackford, 1928; and Evans, 1933) to one in four thousand necropsies (Reifenstein *et al.*, 1947). The clinical incidence was 1 in 10,000 in American Army recruits, and 1 in 12,000 in children under 15 years at Toronto (Mustard *et al.*, 1955).

Sex Incidence. In our series there was a ratio of 5 males to 3 females, but earlier there were more men as several were diagnosed during military service. In the necropsy series of Abbott (1928) and Reifenstein *et al.* (1947) it was four times as common in males, and in most surgical series it has been two or three times as common. There was, however, an equal sex distribution in 44 children (Bonham-Carter, 1954) and in 23 consecutive patients in Helsinki (Halonen *et al.*, 1951). As many are without symptoms and as routine medical examinations are more common in men, the true male preponderance may not be as high as has been thought.

Age of Patients when First Seen. Of our patients, 60 per cent were under 20 and only 14 per cent over 30 years of age (Table I): nine have since passed 30, but this only increases the percentage

TABLE I

AGE INCIDENCE (WHEN FIRST SEEN) OF PATIENTS WITH COARCTATION

	0 to 4	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 55	Total
Males	6	10	10	21	10	12	9	3	1	82
Females	3	8	13	7	4	8	3	1	1	48
Total	9	18	23	28	14	20	12	4	2	130
With aortic stenosis	—	2	—	—	2	—	2	—	—	6
With aortic regurgitation	1	2	4	7	5	4	3	2	0	28
*Percentage with aortic regurgitation	14		18	22	27		28			22

*In calculating this the patients with aortic stenosis have been excluded: three patients who were under observation when aortic regurgitation developed have been included twice—before and after.

to 21, which is less than we expected. This is partly because adult patients are difficult to follow regularly, and are reluctant to return to hospital when they feel well, but if many were still living it seems that more should have been seen for incidental reasons. We cannot recollect seeing anyone for angina pectoris who was then found to have coarctation of the aorta, though we have seen such with dextrocardia, for example. The age incidence of these cases suggests, but can do no more, that there is a heavy mortality from 20 onwards.

Diagnosis

If the blood pressure is taken whenever there is unusual pulsation in the neck (Bramwell, 1947) and if the femoral pulse is felt whenever there is brachial hypertension or unexplained aortic regurgitation few cases should be missed. Bending forward with the arms hanging by the side (Campbell and Suzman, 1947), has proved useful in demonstrating more clearly the collateral circulation in the back. Rib notching is not often seen before 7 or decisive before 10 years but we have seen it clearly at the age of 6 (Fig. 1): it is not always found especially if there is a good collateral circulation elsewhere, but may become extreme (Fig. 2). Other radiological signs are rarely diagnostic but are often interesting and sometimes important: some examples are shown in Fig. 3.

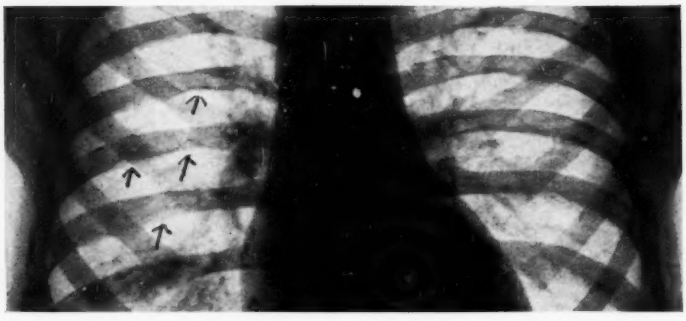


Fig. 1.—Notching of the ribs already clearly visible, especially in the sixth rib, in a boy aged 6 years.

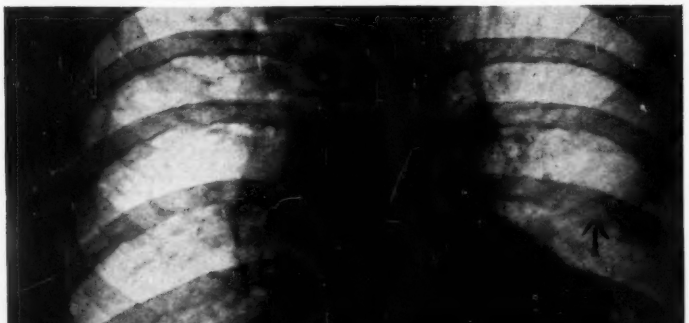
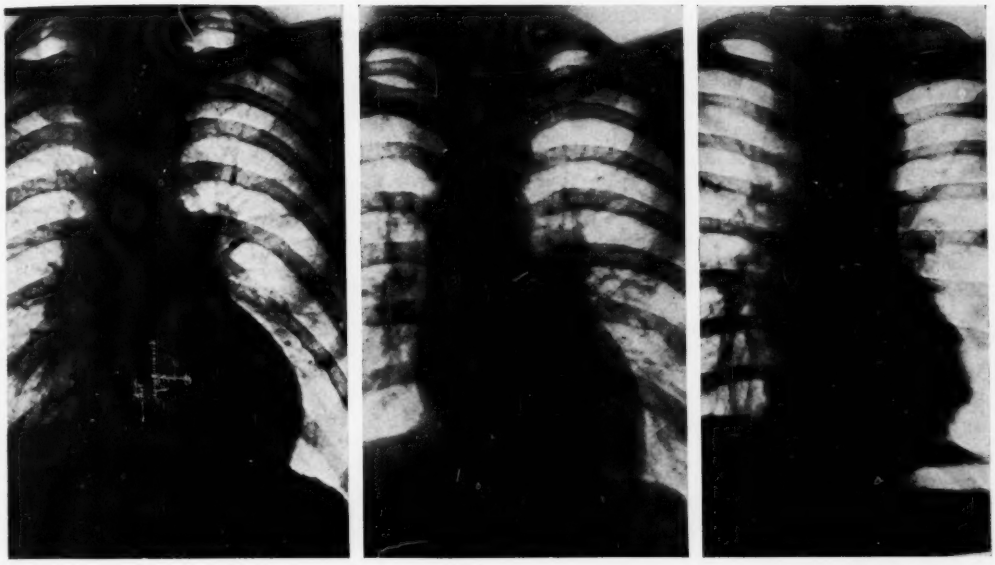


Fig. 2.—Unusually deep rib notching in a woman, aged 52 (Case 21). We do not know of any case where this has led to fracture of a rib, but the tortuous collateral arteries may become aneurysmal and rupture.



A B C

FIG. 3.—Three varying pictures of the region of the aortic knuckle in coarctation. (A) The large left subclavian artery simulates the aortic knuckle. (B) Below the shadow of the left subclavian a second shadow, the descending aorta, is clearly seen. (C) The descending aorta is easily seen and forms a continuous shadow from the site of the aortic knuckle. The heart was not enlarged (c.t.r. 46–49%) in any of these three patients.

A difference of blood pressure of more than 30 mm. between the two arms suggests that the left subclavian is involved in the coarctation or, more rarely, arises below it. Palpable pulsation in the abdominal aorta suggests an abnormally low coarctation. We agree with Granstrom (1951) and Walker and Stanfield (1952) that the retinal arteries show striking corkscrew tortuosity without the usual changes seen in hypertensive retinopathy.

Physique. Several observers have commented on the good physique of patients with coarctation (Newman, 1948) and, in general, we agree, though it is not confined to well-built subjects. We have not proved this by measurements, but an unduly large proportion, women as well as men, have a well-developed chest. Often the shoulders are broad and the muscles stand out prominently. The physique was unusually good in rather more than a quarter of these patients, average or good in about half, and poor in less than a quarter. If patients with coarctation and others with atrial septal defect were mixed, 70 per cent could probably be separated correctly without looking at the pulsation in the neck.

COURSE AND PROGNOSIS

Some of these patients have been seen only for a short time or had resection soon after their first visit, but 80 have been followed on an average for five years and a few much longer. We shall describe the state of those seen in each decade to give an idea of the course and prognosis. School children and men liable for military service are seen more often than older patients without any symptoms simply because of the murmur so our picture of the natural course and prognosis may be biased by this, but otherwise we think it reasonably representative. This seems the only way the question can be answered, for patients can rarely be followed for 30 or 40 years.

Two patients have been followed for nearly 25 years. The first still works and feels well but

has deteriorated through the third decade: the second is still well at 49 though her blood pressure was 220/115 when she was first seen.

*Case 2.** This boy was first seen when he was 7 and was a little breathless; when he was 11, the collateral circulation and rib-notching were obvious. The blood pressure was averaged 147/85 at 7, 176/95 at 11, and 210/110 at 16, without any change clinically or in the size of the heart (c.t.r. 47%). Aortic regurgitation developed between 16 and 21, but there was no change in the pressures till he was 26, when they were 240/90 and for the first time there was some left ventricular strain in the cardiogram. He was unwilling to have an operation. He is now 30 and is at regular work with few symptoms. In spite of the aortic regurgitation, the heart shows no more than fulness of the left ventricle (c.t.r. 48%) but the blood pressure is now 260/90 mm.

Case 3. When she was 25 she became a little breathless after a stillbirth in her second pregnancy: her blood pressure was about 210/110 and sometimes 230/120. Thirteen years later her fourth child was born in Guy's Hospital by Cæsarean section: she made a good recovery and the pressure settled from an average of 235/118 to 205/109 resting in the ward. When she was 46 she thought it was time to stop going out to work as well as doing her own work at home. At 49 she is still leading a normal life, but is a little more breathless; the heart is little changed (c.t.r. 56% instead of 54% when 25), the blood pressure is 250/120 and the cardiogram now shows slight inversion of T in V5 and V6 only.

Course during the First Decade. The occurrence of congestive failure in the first months of life is well-known: a mortality of over 50 per cent has been reported in such infants (Nouaille *et al.*, 1954; Mustard *et al.*, 1955) but Gross (1950) thinks that most of them recover with medical treatment as the collateral circulation improves. One patient sent to us with this diagnosis had, in fact, lymphatic obstruction of the type seen in Milroy's disease.

We have seen 28 patients in this decade and three of them have died. The first was a girl, aged 3, with recurrent attacks of failure (Case 22, q.v.). A boy, aged 7, has probably died, for we watched him getting worse and his heart getting larger during six years: his aortic stenosis and incompetence were most likely rheumatic for we saw him with typical rheumatic nodules and pericarditis (*Case 1*). Towards the end of this decade one girl became increasingly short of breath and a year later was admitted with bacterial endocarditis; although she recovered from this she died soon after with congestive failure (Case 18).

One girl, aged 9, had severe migrainous headaches, one boy, aged 3, with a blood pressure of 142/82, had such severe epistaxis that he needed transfusion, and another girl, aged 3, had a very large heart that we attributed to congenital mitral incompetence: all these have had successful operations, but the last too recently to know if the heart will become much smaller.

With these exceptions most children have come to us for routine examination because of their murmur and have seemed normal to their parents. A few were breathless or easily fatigued, and three complained of headaches that may have been due to berry aneurysms. We have no evidence of any others losing ground during this decade. Most of them are developing well and leading a normal life without symptoms, though generally the blood pressure shows a steady increase. In 8 patients followed on an average for 7 years, the mean pressure rose from 147/98 to 170/106, but in six others there was little rise during four years.

Second Decade. We have seen 50 patients in this decade and watched many of them through most of it, with only one death. This girl died in hospital when she was 17: there was no necropsy and the cause of death was said to be " pneumonia and aortic incompetence," but we think she may have had heart failure (*Case 4*).

For most patients this period is uneventful, though the blood pressure continues to rise. Campbell and Suzman (1947) thought that it rose till somewhere between the ages of 15 and 18 and then stabilized and this is supported by our larger series where the steep rise levels off at about 17 or 18 years (see Fig. 4). In 8 cases, followed on the average for eight years, the mean rise was from 168/99 to 193/108; but there were 7 others with no rise during five years—generally older patients followed from about 14 to 19 years of age.

Cerebro-vascular accidents, however, may start in this decade. Four patients came under

* Cases 1–15 are numbered as they were when reported by Campbell and Susman (1947): Cases 16–28 are shown in Table III.

our observation because of such attacks (see p. 483): two made excellent recoveries but two were left with hemiplegia. Cerebral attacks are less often fatal than in the next decade, but may be so or may leave a persistent hemiplegia.

Apart from these major complications symptoms are not common before the third decade: headaches and dyspnœa on exertion are the most usual. Patients rarely complain about their legs, but from this age onwards some coldness or aching on exertion may be elicited by questioning.

Third Decade. This is very different from the two earlier decades. Of the 37 patients, many still regard themselves as symptomless though more have headaches or cannot do as much as others; most of them are leading normal lives—many even active or athletic lives. In general the blood pressure no longer shows any progressive rise and the majority still have hearts of normal size.

This might suggest that the outlook is still just as good, but 5 of the 37 patients have died and most of these died suddenly or rather suddenly within two or three years of a time when they seemed as well as ever. One died from a ruptured aorta, one from a cerebral hæmorrhage, and two from congestive failure (Cases 16, 17, 15, and 19): all these had been in good health two years before. The fifth was cured of bacterial endocarditis, but developed congestive failure three years later and died after operation (Case 23). Few other patients have lost ground seriously, but in two aortic regurgitation was increasing and leading to progressive cardiac enlargement.

The blood pressure is no longer rising at this age and the average figure shows a steady level at 191/105. Individual patients where we have records over several years show the same result, for 12 followed for four years or more showed no change, and only 3, all followed for ten years, showed any rise.

Fourth Decade. Two of the 17 patients died during this decade—a man, aged 32, who had a very large heart and free aortic regurgitation, and a man, aged 31, who had aortic stenosis and was becoming disabled, though the immediate cause of death was resection (Cases 20 and 24). The numbers are large enough to suggest this is a safer period and that most of those with the greatest risk of rupture of the aorta or of cerebral hæmorrhage die during the third decade.

In general, the others are doing well and few of them have increasing symptoms. The only patient we have seen with atrial fibrillation, and it was paroxysmal, was of this age and it has become no worse during four years.

In the early thirties the average blood pressure was no higher than in the twenties, and the slight rise towards the end of this decade is of doubtful significance for the numbers are smaller. Of the 7 individual records available over some years, only one showed much change. His pressure rose from 180/110 to 200/125 between 27 and 31; he was leading a most energetic life loading and driving lorries for long hours, and since he has taken life more easily there has been no further rise in five years.

Fifth and Sixth Decades. There are not enough patients in this period for generalizations. The small number suggests a higher mortality in the previous decade than do our direct observations. Most of the survivors have a high blood pressure and there is a slight increase in the average figure (220/122) after a period of stability, but the numbers are too few to be significant. One woman had a blood pressure of 235/110, a large heart (c.t.r. 56%), and free aortic regurgitation so that we hardly expected her to do well, yet five years later she was very well with no change. Case 3, who has been followed from 25 to 48 is still well though her blood pressure is now 250/120. In a third the blood pressures were lower, 178/92, and had not changed for 23 years.

The oldest patient was first seen when she was 52 and was admitted to hospital with pneumonia: shortly before there had been an episode suggestive of left ventricular failure; her blood pressure remained about 217/128, but these episodes became increasingly troublesome and she died with congestive failure when she was 55 (*Case 21*).

Conclusions about Rise of Blood Pressure with Age. These are shown in Fig. 4 and Table II. Patients with aortic stenosis have been excluded, but not those with aortic regurgitation (see p. 486). and those followed ten years or more have been included twice. The systolic pressure rises much

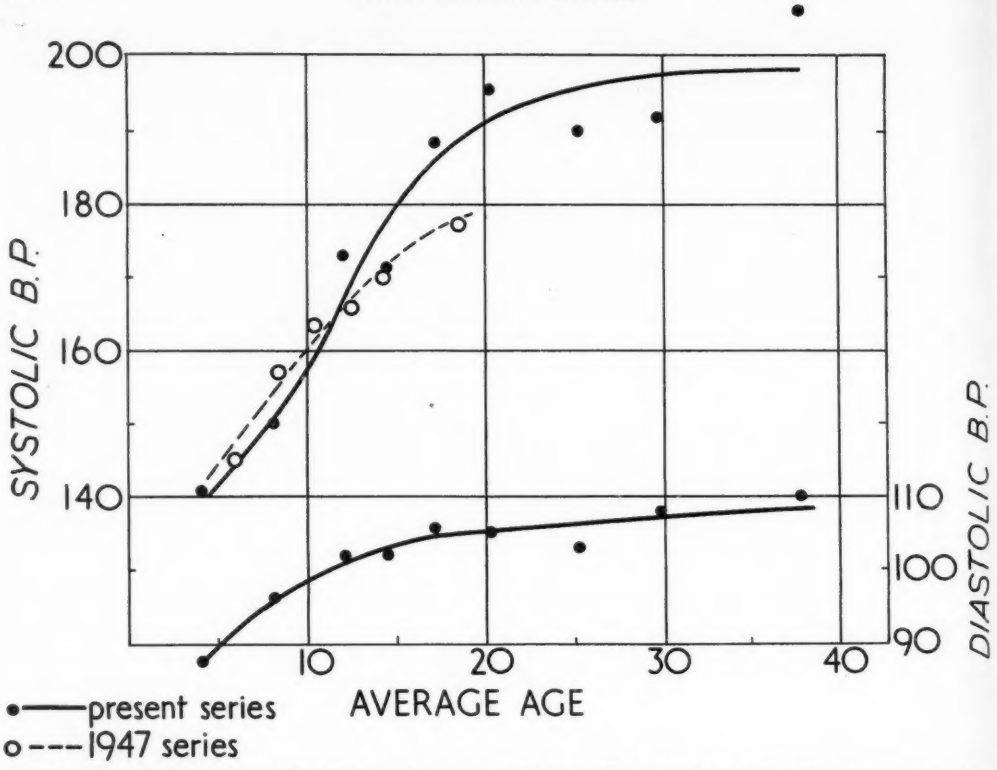


FIG. 4.—The rise of systolic and diastolic blood pressures with age. The curve for the diastolic pressure (below) is of the same shape as the curve in normal subjects, about 30 mm. higher throughout. The curve for the systolic pressure (above) has the same general shape but rises more sharply than the normal curve, so that it is 55 mm. above normal at 5 years and 75 mm. above normal after 20 years of age. The dotted line represents the curve for the systolic pressures reported by Campbell and Suzman (1947) from their own and other reported cases.

TABLE II

BLOOD PRESSURE IN COARCTATION OF THE AORTA RELATED TO AGE

	Average Age	Blood Pressure	
		Systolic	Diastolic
Youngest 15 patients	4·4	141	87
Next 15	8·1	150	96
Next 15	11·5	173	102
Next 15	14·2	171	102
Next 15	17·3	188	106
Next 15	20·7	195	105
Next 15	25·9	190	103
Next 15	29·3	192	108
Oldest 15 patients	37·5	206	110

The patients have been arranged in order of age and grouped in fifteens to minimize individual variations.

more than the diastolic, 55 mm. against 20 mm. from 5 to 35 or 40 years. The rise is not regular: both rise more steeply and fairly regularly until about the age of 17 and then level off and rise very slightly, if at all.

The blood pressure on a smoothed curve rises from 140/87 at the age of 4, to 154/93 at 8, to 169/99 at 12, to 184/104 at 16, and to 193/105 at 20; and only to 197/107 at the age of 30 years.

Conclusions from Patients who have Died. Of the 16 patients who have died (see Table III) 4 give us no information as they were in good health and died unexpectedly after operation. Of the other 12, six were seen because they were already seriously disabled so do not help much in judging the prognosis but the other six were in good health when they were first seen and three were sent only because of a routine medical examination (Case 4, see p. 478; Cases 15–19 see pp. 482–484): there was, therefore, no reason to anticipate their deaths yet they all died within two or three years. The unexpected deaths of these six, mostly in the third decade, has been the main reason for making us think that operation should be advised for most young patients.

Hazards of Coarctation

In cases that have survived infancy, the main causes of death during the first three decades are aortic rupture, bacterial endocarditis or aortitis, and intracranial hæmorrhage. After the age of 30 the incidence of congestive heart failure rises, sometimes without complications, sometimes after bacterial endocarditis, but most often when there is aortic regurgitation. Our patients illustrate all these hazards (Table III). After 40 there is about an even chance of death from an incidental cause.

TABLE III

Some Findings in Patients with Coarctation who have Died

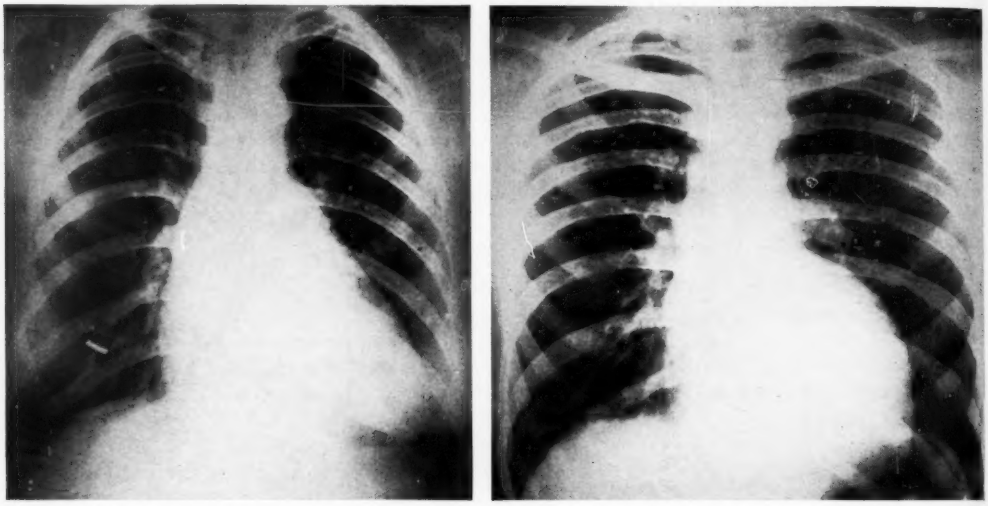
Case No.	Age and sex	B.P.	Aortic valve	C.t.r (%)	Cause of death	Aortic valve cusps	Other findings at necropsy, if any
1	M13	165/60	A.S.A.I.	68	?Rheumatic H.D.	—	No necropsy
4	F 17	200/90	A.I.	56	"Pneumonia and A.I."	—	No necropsy
15	M27	172/109	A.I.	48	C.H.F.	—	No necropsy
16	F 22	210/110	(A.I.)	61	Ruptured aorta	?3	Aortic cusps thickened
17	M27	190/85	(A.I.)	54	Cer. hæmorrhage	2	Aortic cusps thickened and incompetent
18	F 9	170/105	?A.S.	61	Failure after S.B.E.	—	No necropsy
19	F 28	204/106	(A.I.)	50	C.H.F.	—	No necropsy
20	M32	190/101	A.I.	66	?C.H.F. ?S.B.E.	—	No necropsy
21	F 55	217/128	N	52	L.V. failure	—	No necropsy
22	F 3	172/143	N	71	At operation*	3	198 g. Valves thickened: bicuspid pulm. valve
23	M26	200/115	N	58	At operation*	3	L.V. much hypertrophied
24	M31	155/110†	A.S.	60	Aneurysm at site of anastomosis*	3	Aortic valve stenosed (Fig. 8)
25	F 11	190/100	(A.I.)	51	At operation*	3	140 g. Nothing else
26	F 13	180/102	N	53	Cer. hæmorrhage*	—	No necropsy
27	F 14	185/95	N	48	Hge. from graft*	2	240 g. Nothing else
28	M17	210/111	N	48	Acute enteritis*	3	455 g. Small diverticulum in septum only

† Systolic pressure in left ventricle, 198. * Died after operation.

In the 304 cases that came to necropsy in the combined series of Abbott (1928) and Reifenstein *et al.* (1947) the main causes of death were as follows. Over one-quarter (29%) died from incidental causes not connected with the coarctation, but this group is not represented in our series. Just over one-quarter (26%) died from congestive failure which is more prominent in our series. Less than one-quarter (21%) died from aortic rupture. The last quarter of the deaths were equally divided between intracranial hæmorrhage (12%) and bacterial endocarditis (12%).

Rupture of the Aorta

One of our patients died from this cause. The first part of the aorta was prominent on X-ray examination (Fig. 5A) and this may perhaps give some warning of the risk; otherwise, it cannot be foreseen for as a rule the blood pressure is not specially high (Reifenstein *et al.*, 1947).



A B

FIG. 5.—(A) A large heart (c.t.r. 61%) from a woman, aged 20, with coarctation. The first part of the aorta was unusually prominent and she died with a ruptured aorta two years later. (B) A large heart with a rounded left ventricle (c.t.r. 54%) from a man, aged 21, with coarctation and aortic stenosis.

Case 16. A woman, aged 20, had always been a little breathless and had aortic regurgitation with a blood pressure of 210/110. She remained well for two years but suddenly became unconscious and died shortly afterwards. At necropsy, the arch of the aorta was thin and aneurysmal and there was a rupture at this site, presumably due to a dissection as the pericardial sac contained 600 ml. of blood. The aortic cusps and the anterior cusp of the mitral valve were somewhat thickened.

In one girl, aged 11, the aorta was difficult to sew up at operation, probably because of the poor quality of the media, so there may have been a risk of aortic rupture (Case 25). Rupture often occurs through a dissecting aneurysm but sometimes through a pre-existing saccular aneurysm. Two of our patients had such aneurysms. One had a large aneurysm proximal to the coarctation, both successfully resected (Brock and Graham, 1952), and the other had a calcified aneurysm just below it (Case 23). In the series of Clagett *et al.* (1954) there were 11 instances of aneurysms distal to, and only 2 proximal to the coarctation: in general, they found the aortic medial changes greater in men.

Aortic rupture occurs at two sites, proximal to the coarctation but generally in the ascending aorta rather than just proximal, and less often distal to it. Among the 304 cases in the series of Abbott and of Reifenstein there were 56 instances of the former and 16 of the latter.

Proximal rupture starts as a dissecting aneurysm: it is associated with medial degenerative changes or rarely with infective aortitis, e.g. in 2 of the 56 quoted. It may occur at any age but mainly in the second and third decades. Among 141 patients under the age of 40 with dissecting aneurysms, 99 of whom died from aortic rupture, Schnitker and Bayer (1944) found coarctation of some degree recorded in 45—in 19 of the 27 aged between 11 and 20, and in 17 of the 53 aged between 21 and 30 years.

Spontaneous rupture of the ascending aorta is the main hazard of pregnancy in patients with coarctation, and was responsible for 6 of 11 cases where death was directly associated with pregnancy (Rosenthal, 1955), in one during labour and in the rest during the third trimester. In Schnitker and Bayer's series there were 92 males and 49 females, and 24 of these 49 were or just had been pregnant and 15 were in the third trimester: the blood pressure was not as a rule known to be specially high and they suggest that metabolic factors during pregnancy predispose to cystic medio-necrotic changes in the aorta.

Distal rupture occurs spontaneously and from endo-aortitis. The latter occurs mainly in the first two decades, and in the 8 cases reviewed by France *et al.* (1950) 6 were under 18, the average age at death being 17 years. In Abbott and Reifenstein's 16 cases, aortitis was present in 6 at least. Spontaneous rupture occurs from rupture of aneurysms, sometimes traction aneurysms at the site of the ligamentum arteriosum (Monckeberg, 1907), or through a jet lesion (Bellet and Gelfand, 1952) or from mucinous medial degeneration (Zaslow and Krasnoff, 1943). In contrast with the aortitis group, the average age at death in ten cases was 37 (France, 1950), only one being under 18 years. No instance of distal rupture has been recorded with complete aortic atresia.

Intracranial Hæmorrhage

This is responsible for about one death in eight. Two of our patients died from this cause, one the day after operation when there was a temporary rise of blood pressure (Case 26).

Case 17. A man, aged 27, had coarctation (B.P. 190/85), aortic regurgitation, and familial polyposis of the colon; in view of the risk of this becoming malignant, he had colectomy, which was well borne. But 18 days after his discharge, he had a sudden agonizing headache and died a few hours later. Necropsy confirmed a large hæmorrhage that had disrupted the right internal capsule but had not broken through into the ventricle. The aortic valve was bicuspid and incompetent.

Apart from the danger of death there is the risk of residual cerebral damage, sometimes with hemiplegia. Among our 80 patients followed for an average period of five years, only one, a girl aged 13, has had a cerebral episode. When sitting at tea she dropped a cup and said she had a severe headache, and stumbled on the way to bed. The headache persisted for a day, and the left arm and leg felt numb. She had quite recovered in three days except for numbness and tingling in the leg which was more sensitive to pain. When she was seen the blood pressure was no higher than usual, 145/90: four years later it was lower, 138/87, and she has continued to lead a normal life.

Four other patients had episodes of this type before we saw them—two with a less satisfactory outcome. A girl, aged 15, had signs of meningeal irritation and the cerebro-spinal fluid was blood-stained and under increased pressure: her blood pressure was always labile and rose to 190/110 with very gentle exercise. A man, aged 28, had a subarachnoid hæmorrhage soon after his recovery from bacterial endocarditis. Both made good recoveries and have had successful resections since.

A boy, aged 19, was admitted with a blood pressure of 260/120 instead of the usual 197/116 and with hemiplegia which persisted: four years after resection he is getting on well with a pressure of 157/95. A girl, aged 13, had frequent headaches and one severe attack was followed by loss of consciousness and a left hemiplegia; coarctation was diagnosed and she had a successful resection: six years later she is well with a blood pressure of 133/92 instead of 185/120: her leg has recovered but her left arm is of little use. Earlier diagnosis and treatment could probably have prevented these two tragedies.

Intracranial hæmorrhage is due in about half the cases to berry aneurysms that can be demonstrated pathologically, and rarely to mycotic aneurysms. Unlike aortic rupture, it shows some correlation with the level of the blood pressure (Reifenstein *et al.*, 1947). Death from intracranial hæmorrhage is most common in patients between 10 and 30 years of age; there was only one earlier than this among the 31 cases of Abbott and of Reifenstein, and in 11 proven ruptured berry aneurysms in association with coarctation, the youngest was 13 years old (Wright, 1949).

Bacterial Endocarditis and Aortitis

These were responsible for another one-eighth of the deaths in the combined series, a proportion that has now been greatly reduced though not abolished. They still, however, cause death indirectly, from congestive failure after the infection has been cured.

Case 18. A girl, aged 9, had not been able to do as much as usual for three years. Additional aortic stenosis was suspected as there was a striking murmur and thrill in the aortic area and a large heart (c.t.r. 61%) with S–T depression from V2–V6, but the blood pressure was 174/98. Operation was advised but there was some delay and she was admitted elsewhere with bacterial endocarditis (blood culture positive, hæmoglobin 33%, an added aortic diastolic murmur, and B.P. down to 140/70). She seemed to have recovered after prolonged treatment with penicillin when she went home five months later, but was back in three weeks with congestive failure from which she died a month later. There was no necropsy.

Two other patients developed bacterial endocarditis during the period of follow-up, one year and six years after they were first seen; both made good recoveries. Two others were sent to us just after treatment for bacterial endocarditis because this led to the recognition of their coarctation. Another (Case 23) had bacterial endocarditis three years before he came to us with congestive heart failure. In three cases the causative organism was *Streptococcus viridans* but in the other three blood cultures were repeatedly negative.

Endocarditis is mainly a hazard of bicuspid aortic valves, and may be followed by free aortic regurgitation and cardiac hypertrophy (Reifenstein *et al.*, 1947). No follow-up study of successfully treated cases has been found, and there was only one instance of coarctation in 442 cases of treated bacterial endocarditis (Cates and Christie, 1951).

Aortitis occurring alone was the cause of death in 6 per cent of Reifenstein's series, the predominant sites of infection being the aorta just distal to the coarctation and the ascending aorta: it was frequently found with endocarditis.

Congestive Heart Failure

This was the commonest cause of death in our series—in 8 patients, if we include two already ill, who died after operation. The girl, aged 3, had an unusual coarctation (Case 22). Two, aged 9 and 24, had failure after recovering from bacterial endocarditis (Cases 18 and 23). The man aged 32 had aortic stenosis also (Case 24). Of the other four, aged 17, 27, 29, and 55, the three younger ones all had aortic regurgitation. Notes of the two who were in good health when they were first seen and of the unusual infant follow.

Case 15. A man, aged 25, had no symptoms and was diagnosed on his discharge from the Navy. He had aortic regurgitation, though the diastolic pressure was high (B.P. 172/109) and the heart was not enlarged. Two years later he became ill and died within three months, probably from congestive failure, although when seen he had been leading a normal life.

Case 19. A woman, aged 26, seen during her first pregnancy, remained well for two years but then developed congestive failure. She was very anæmic but bacterial endocarditis was not confirmed. A loud aortic diastolic murmur, without much change in the pulse pressure (200/100 instead of 203/109), was heard for the first time. Her anæmia improved very slowly and some congestive failure persisted, but after three months in hospital she was allowed to go home. She died soon afterwards and there was no necropsy.

Case 22. A girl, aged 3, had recurrent congestive failure for 18 months. The striking pulsation in the neck seemed to exclude aortic stenosis, which was suspected because the pressure was not high enough to explain the very large heart and recurrent failure. At operation the pressure was 168/79 in the left ventricle and 172/143 in the first part of the aorta, though it had been 130/95 in the brachial arteries. The first part of the aorta was dilated but became narrowed and obstructed before the origin of any aortic branches. At necropsy, the heart weighed 198 g. and the left ventricle was greatly hypertrophied. The aortic valve was thickened but not stenosed: the pulmonary valve was bicuspid.

Congestive failure is uncommon in young patients in the absence of some additional lesion. Among the 19 patients dying in failure in Reifenstein's series, 18 had coincident valvular, coronary arterial, or some cardiorenal disease; the average age at death was 39 years and only one was under

20; and all six in whom the duration of failure was a year or less had advanced deformity, usually stenosis, of the aortic valve. Our patients show that coarctation with no complication except aortic regurgitation may lead to congestive failure by the third decade.

Coarctation at or Above the Origin of the Left Subclavian Artery

Brown (1950) states that this is rare as only 20 cases had been recorded, but many more have been found in recent series. When the origin of the left subclavian artery is involved in the coarctation its recognition is of surgical importance, and is suggested by *consistent* differences of pressures in the right and left brachial arteries.

Differences of 20 mm. are not significant. We have, for example, found consistent differences in several patients, e.g. 210/110 and 190/110, 210/130 and 195/125, 235/118 and 220/112—the highest reading in each of these being in the right arm. Such differences do not militate against successful operation, e.g. readings of 215/106 and 194/105 became 182/93 and 159/90 after a resection.

Large differences are, however, of great significance. In one patient in whom no operation was possible owing to the relationship of the aortic branches to the coarctation, no difference was recorded between the two arms and the *right* subclavian was the last branch before the coarctation; but in the other, the readings in the right arm were 184/118 and in the left 125/104, and this warned us of the involvement of the left subclavian in the coarctation and of the difficulty of operation which, in fact, proved insuperable in 1950, though it may be overcome by grafting. In another boy, the pressure averaged 162/107 in the right, and 130/97 in the left arm; he had few symptoms and after an aortogram in 1949 operation was not advised as the left subclavian seemed involved in the coarctation: six years later his condition is unchanged.

The last two were good examples of unilateral rib notching, though in the former there was slight notching of one rib on the left side as well as the major notching on the right side (Fig. 6). Valdoni (1955) finds that the pressure is higher than usual when the collateral circulation depends on one side only.

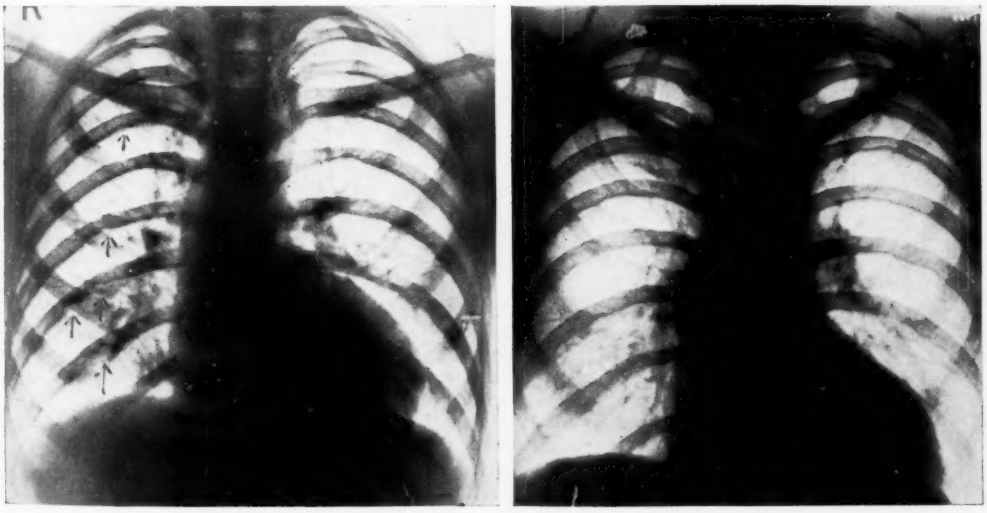


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Fig. 6.—(A) Rib notching that is mainly on the right side: the left subclavian was involved in the coarctation and the blood pressure was 184/118 in the right and 125/104 in the left arm. (B) A large heart (c.t.r. 58%) from a man, aged 33, with coarctation and calcification of the stenosed aortic valves. The dilatation of the first part of the aorta is characteristic of congenital aortic stenosis but is not seen in Fig. 5B.

Exceptionally, the difference may be the other way round or both subclavians may be obstructed. The readings averaged 162/100 in the right and 177/110 in the left arm in one case, and 140/110 in the right and 190/100 in the left arm in Case 25: the right subclavian (3 mm. in diameter) arose below and behind the large and dilated left subclavian from a very small projection of the aorta above the coarctation, which was 1 cm. long.

The origins of both subclavians were obstructed, partly by thrombosis, near the coarctation and the blood pressure was 200/115 in the temporal artery at a time when it was only 130/90 in the brachial arteries in Case 23 who died after operation.

Aortic Regurgitation and Coarctation

Some degree of aortic regurgitation was indicated by a diastolic murmur in nearly a quarter of these patients. It is, we think, most often due to a bicuspid aortic valve that has become atherosclerotic. Generally, it is slight and the murmur is a soft one, there is no water-hammer pulse, and the pulse pressure is no wider than usual. We soon found that the diastolic pressure was higher than in other forms of aortic regurgitation, and that it was rarely below 100, though in the course of years the usual picture with a wide pulse pressure and a low diastolic pressure may develop. This is well shown in Fig. 7, relating the systolic and diastolic pressures, for most of those with aortic regurgitation (shown by the white circles) fall among the others, and are absent only from the narrow upper margin showing patients with relatively high diastolic pressures: there are only 4 patients with regurgitation standing out below the lower margin of the general scatter, where the diastolic pressure was low because the regurgitation was more significant.

Excluding the six patients with aortic stenosis, some of whom had regurgitation also, 28 of 124 patients had aortic regurgitation. This incidence of 23 per cent is not much below that of bicuspid

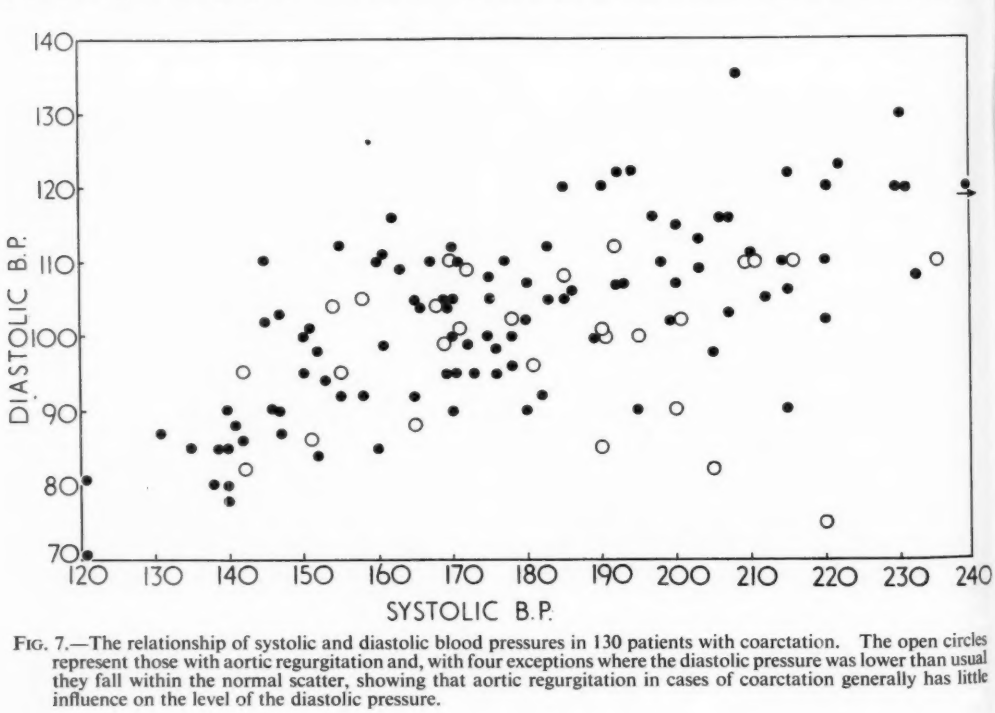

Fig. 7.—The relationship of systolic and diastolic blood pressures in 130 patients with coarctation. The open circles represent those with aortic regurgitation and, with four exceptions where the diastolic pressure was lower than usual they fall within the normal scatter, showing that aortic regurgitation in cases of coarctation generally has little influence on the level of the diastolic pressure.

aortic valves, from 25 (Abbott, 1928) to 42 per cent (Reifenstein *et al.*, 1947). It increases with increasing age; being present in 16 per cent of those under 15, in 22 per cent of those between 15 and 19, and in 27 per cent of those over 20 (see Table I). Sometimes we know when the regurgitation developed. In Case 2, it was between 16 and 21 without any immediate change in the blood pressure though it widened from 210/110 to 260/90 during the next eight years; in Case 19 between 26 and 28, the pressure changing only from 203/109 to 200/100; and in another man between 18 and 21 years of age, the pressure changing from 200/100 to 218/100.

It is, therefore, possible for atherosclerotic bicuspid valves to become incompetent early in life. This is more important than a specially high blood pressure or the effects of rheumatic infection. The way in which the diastolic murmur may at first be faint, heard at one visit and not at the next, and the age incidence are not suggestive of rheumatic disease and fit in better with bicuspid valves gradually becoming incompetent.

When patients with coarctation have aortic valve disease, it has often been attributed to a rheumatic infection both by clinicians and by pathologists. In our view, however, this is uncommon. Among the 130 patients there are only 8 who gave a history of rheumatic fever. It is true that four of these had aortic regurgitation and a fifth had pure aortic stenosis but this was thought to be congenital at necropsy, and there was no valvular disease in the others. Even more important there was no clinical or pathological evidence of mitral stenosis in these or in any of the patients with aortic valve disease, and it was present in only 4 per cent of the necropsies in Reifenstein's series. We cannot be certain that all our patients were asked about a past rheumatic history, but if some were omitted, we doubt the correctness of the rheumatic history in others, who were kept in bed because of a systolic murmur and not because of joint pains; and it may well be that hearing this murmur and failing to diagnose coarctation was the reason for thinking them rheumatic.

Aortic Stenosis and Coarctation

This combination has been emphasized by Taussig (1947) and by Smith and Matthews (1955) who collected 24 reported cases with necropsies; it was present in 6 of our patients, more often than would be expected by chance.

Case 24. A man, aged 31, had been getting worse for two years. The heart was large (c.t.r. 60%) and the blood pressure was 155/110 in both arms but 198/36 in the left ventricle. His coarctation was resected and his aortic valve divided, but he died four weeks later. The mitral valve was normal and the aortic valve had two large cusps and one small cusp, all much thickened and fibrosed with a large fibrous calcified mass between two of the cusps (Fig. 8).

A man, aged 21, has coarctation (B.P. 158/109; c.t.r. 54%; Fig. 5B), signs of aortic stenosis, but few symptoms. A man, aged 23, has coarctation (B.P. 153/102; c.t.r. 53%) and fairly severe aortic stenosis with some anginal pain. A man, aged 33, is still getting on well, though he has a blood pressure of 175/100, a large heart (c.t.r. 58%), and aortic stenosis with calcification of the valve (Fig. 6B). A girl, aged 9, has been described (Case 18). In the sixth (Case 1) we thought that the stenosis was rheumatic. The last five all had some aortic regurgitation as well.

Association with Other Congenital Abnormalities

With Other Cardiac Abnormalities. We have not seen many other additional lesions except in the arrangement of the aortic branches. One cyanotic girl, aged 9, had Eisenmenger's complex also (Campbell and Cardell, 1953). A girl, aged 5, was thought to have transposition of the great vessels as well. A boy, aged 16, had coarctation (B.P. 180/110), an enormous heart (c.t.r. 75%), loud systolic and diastolic murmurs at the apex, and atrial fibrillation: the diagnosis of congenital mitral incompetence (and stenosis) was supported by catheterization. A boy, aged 7, had pulmonary stenosis with a systolic gradient of 28 mm. and slight coarctation (B.P. 130/84). A girl, aged 16, with recent atrial fibrillation was found to have slight mitral stenosis, bilateral S.V.C., a pulmonary vein that drained into the right S.V.C., and slight coarctation (B.P. 130/85). Two patients, one with Fallot's tetralogy (Case 15, Brinton and Campbell, 1953), and one with a patent ductus (Case 23, Campbell, 1955), were found at necropsy to have a trivial coarctation. These seven have not been included.

The following have been included as coarctation was the main lesion. One man, aged 23, who had a successful resection, had a loud systolic murmur and thrill in the pulmonary area and a pressure gradient

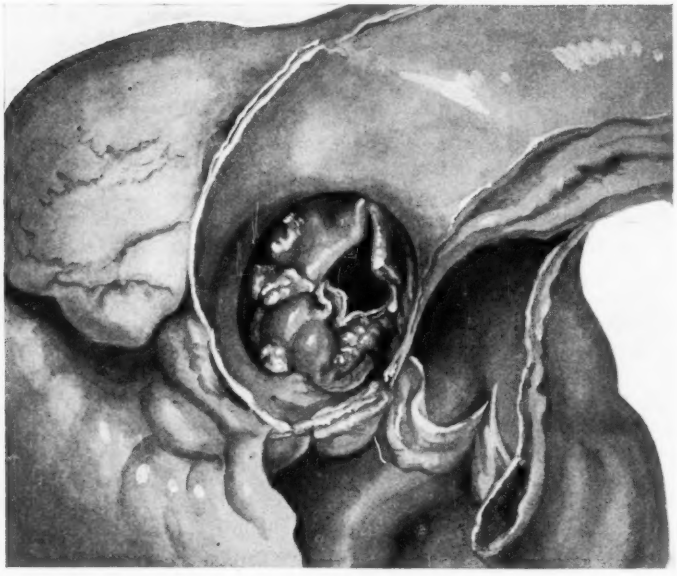

FIG. 8.—A heavily calcified and stenotic aortic valve that had been divided three weeks before his death, from a man, aged 31, with coarctation. Case 24.

of 11 mm. across the pulmonary valve—hardly enough by itself to prove stenosis, but probably enough with the physical signs. Wood (1950) has reported one patient with coarctation and a ventricular septal defect. We think this combination is uncommon: it was suspected in three of our patients, but catheterization showed no abnormality in two, while in the third a pulmonary vein drained into the superior vena cava.

We have seen only three patients with a patent ductus in addition, although this is found in 10 per cent of some series. In one boy, aged 2, a blood pressure of 140/70 was accepted as due to a large patent ductus, which from the site of the murmur was thought to be on the right side: when he was 7 it was heard best on the left, the pressure had risen to 175/105, and coarctation was recognized.

With Turner's Syndrome. Turner (1938) described the syndrome of a webbed neck, cubitus valgus, and infantilism—a sub-variety of ovarian agenesis, now more commonly known as gonadal dysplasia (Polani *et al.*, 1956). Albright *et al.* (1942) first drew attention to the association of coarctation with this syndrome. Three of our four apparently female patients with Turner's syndrome are included in a series of gonadal dysplasia where the chromatin sex has been determined by Polani *et al.* (1953) on skin, blood, or both, and all three are chromosomal males. Of the 54 patients with gonadal dysplasia investigated by Polani (personal communication) or recorded by Grumbach *et al.* (1955) 49 have male and 5 female chromosomal sex: webbing of the neck was present in 31 and coarctation in 12 of these. All those with coarctation and gonadal dysplasia were chromosomal males and had also a third abnormality, notably webbing of the neck.

There were not many with *other non-cardiac congenital defects.* One girl had bilateral cervical ribs, and one man had had a successful operation for hypospadias. One girl had lymphatic swelling of the legs and she had ptsosis of the left eye-lid also, and another had bilateral nerve deafness. Nor have we often found a family history of other defects. The mother of one patient had a patent ductus and the daughter of another had pulmonary valve stenosis, and since writing this we have seen the sister of one of our patients also with coarctation. Bonham-Carter informs us that he has seen two siblings, both with coarctation, a patent ductus, and an aberrant subclavian artery.

THE SIZE OF THE HEART

Bonnet (1903) pointed out that the heart might be of normal size: it may remain so over many years even when the blood pressure is very high (Lewis, 1933). Brown (1950) stated that it might

be normal in size or slightly enlarged, or sometimes when there was aortic regurgitation greatly enlarged.

It is surprising how many patients have small vertical hearts, though generally there is some fulness of the left ventricle on radioscopy. The large well-developed chest is only part of the explanation. Some increase is quite common but large hearts are uncommon. In considering size we have omitted 8 cases with complications: six had aortic stenosis and in a seventh this was suggested by the left ventricular strain but other evidence supported mitral incompetence, while the eighth had recurrent heart failure in infancy (Case 22). The heart was only moderately large in two of these (c.t.r. 53–54%) but large in three (c.t.r. 58–61%) and enormous in three (c.t.r. 68–71%).

There were 128 other patients, a few who had been followed for ten years being included in two decades. Most have normal or even small vertical hearts, nearly two-thirds having cardiothoracic ratios of 50 per cent or less, nearly half of 48 per cent or less, and nearly one-third of 46 per cent or less (Table IV). Age alone did not have a great influence though the smaller hearts were less common in those over thirty: they were found in patients with very high blood pressure and in others with aortic regurgitation but not when this was severe.

TABLE IV

THE SIZE OF THE HEART IN COARCTATION OF THE AORTA

Age in years	No. of cases	Percentages with cardiothoracic ratios of			
		48 and less	49–52	53–56	57 and over
0–19	73	50	34	16	0
20–29..	36	52	22	17	9
30 and over	19	26	32	32	10
Total	128	47	30	19	4

At the other extreme there were only 14 (11%) with ratios of 55 per cent or more, and in 9 of these it was only 55 or 56 per cent: 3 of these 9 were over 30 and 4 of the 6 under 30 had aortic regurgitation. Of the 5 with larger hearts (c.t.r. 57% or more), 4 had aortic regurgitation: one developed a larger heart (c.t.r. 51% at 22 to 57% at 29 years, with a blood pressure of 220/75): one woman, aged 39, with a large heart (c.t.r. 57%) was just as well after five years with no further increase; the third (c.t.r. 61%) died two years later with a ruptured aorta (Case 16); and the fourth, aged 32, with the largest heart (c.t.r. 66%) and free aortic regurgitation died a year later (Case 20). In the fifth his congestive failure and large heart (c.t.r. 58%) had followed bacterial endocarditis (Case 23).

Few patients showed any increase while under observation, but this happened in two, both with aortic regurgitation. One has just been mentioned and in the other it increased between 15 and 20 years of age (c.t.r. 49 to 53%), although he seemed as well with no change in the blood pressure, 165/89: he showed unusual dilatation of his descending aorta (Fig. 3C). Both these patients should have had an operation when they were first seen, but at that time we regarded aortic regurgitation as a contra-indication.

It is clear that most patients continue to have normal hearts for many years in spite of the high blood pressure, sometimes even with the lesser degrees of aortic regurgitation. Sometimes, after thirty, the heart may become large even without any regurgitation.

ELECTROCARDIOGRAPHIC CHANGES

Lewis (1933) stated that there was generally left axis deviation but 4 of his 6 cases were over 40: Campbell and Suzman (1947) were surprised to find a normal axis as common as left axis deviation. Brown (1950) says " There are no characteristic changes in the electrocardiogram which is often

physiological. Ultimately there is the picture of left ventricular hypertrophy." We thought these views were due to the use of standard leads only but they are confirmed by chest leads. We have omitted the same 8 patients, mostly with aortic stenosis, all of whom had some, often severe, left ventricular strain.

Among the other 120 patients, more than one-quarter had normal electrocardiograms, often in spite of a high blood pressure for a long time, but this was uncommon when there was aortic regurgitation as well. Half had some left ventricular preponderance, and nearly one-quarter had some strain, but generally no more than a little S–T depression or minimal T inversion in leads V5, V6, or V7 (Fig. 9).

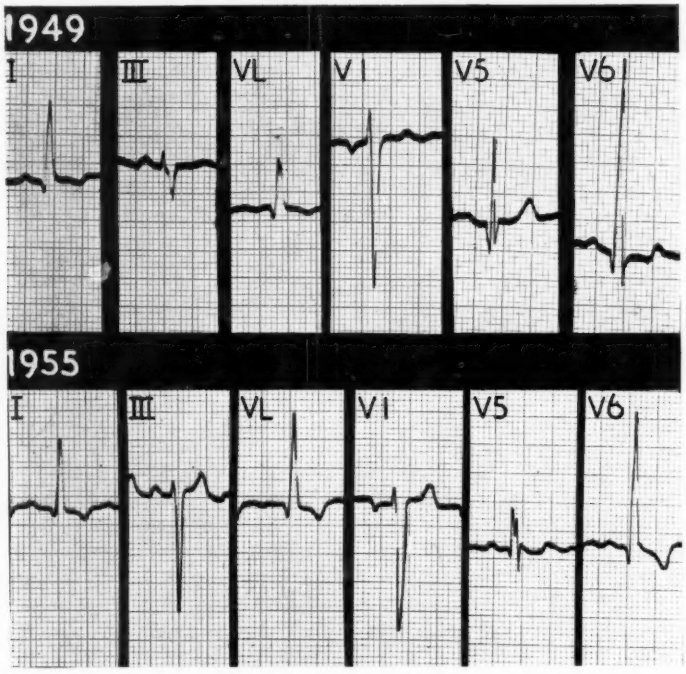

FIG. 9.—Increasing left ventricular strain in a patient aged 22, where the heart had also become larger. (A) In 1949 with slight S–T depression and a late-rising T wave in V6. (B) In 1955, with a biphasic instead of a large upright T in V5 and with moderately deep T inversion in V6.

We had diagnosed preponderance on a prominent S in V1 and a prominent R in V6 without exact measurements, but this is a lower criterion than is generally accepted. If S in V1+R in V6 must be 35 mm. for the diagnosis of left ventricular preponderance the number would be much less, though S in V2 was often larger than in V1 and would bring more cases up to the required standard.

Slight left ventricular strain may occur from the second decade onwards, but is much more common in patients over thirty, when normal cardiograms are less common. Slight aortic regurgitation did not have much influence, but as it became more severe it was more often associated with left ventricular strain (Fig. 9). The youngest patient with the strain pattern was 18; he was almost without symptoms but the flat T waves in V5 and V6 were one reason for advising resection and became upright after it: ventricular strain in young patients is, we think, a special indication for resection.

The Results of Surgical Treatment

Most patients with coarctation are enjoying good health with few symptoms, so an operation that carries a considerable risk is not easy to advise; yet disaster may arrive with little warning and a successful resection improves the outlook for the future. It is easier when there are serious symptoms or an unusually high blood pressure, or when the patient is young and the risk less. But the diagnosis is still made late in many patients, sometimes only when symptoms are severe or even when there is heart failure. We have come to think that operation should be advised in most children, that after the age of 8 if not sooner there should be no delay, and that early aortic regurgitation is an added reason, for the natural prognosis seems less favourable than we had supposed. Crafoord (1955) rarely recommends surgery before 5 or 10 years, but thinks it should be urged for all patients under 20, advised for most between 20 and 30, but needs careful consideration after that age. He, too, looks on aortic regurgitation as an indication, particularly when the heart is not greatly enlarged.

During the last eight years 46 patients with coarctation have been operated on, all except two by Sir Russell Brock at Guy's Hospital. Ten were between 10 and 14, nine between 15 and 19, and nine between 20 and 24 years. Most of them (60%) were, therefore, between 10 and 24 years of age, but eleven were older and seven were younger. Clearly they were not all of the ideal age and this will be a problem for some time. Most of them had been under observation before operation, sometimes for several years.

Operative Mortality. Seven of the 46 patients died but 3 of these were among the 9 admitted directly under Sir Russell. It seems fair to exclude these three since two had recurrent congestive failure (Cases 22 and 23) and in the third the coarctation could not be resected at a previous thoracotomy (Case 25), and if so, the mortality was 9 per cent. In 648 resections that we have reviewed the mortality was 7 per cent, but many authors, including ourselves, think that it is now about 5 per cent in cases without complications: Gross (1953) has reported only two deaths in his last 100 cases.

Four of the deaths were particularly unfortunate as the operation seemed successful, but one died from fulminating enteritis soon after it (Case 28), one from hæmorrhage through a branch of the graft (Case 27), one from subarachnoid hæmorrhage following a rise of blood pressure to 200 the day after it (Case 26), and one from an aneurysm at the anastomosis associated with a staphylococcal septicæmia (Case 24). The last two occurrences have been reported in other series and suggest the need for prophylactic antibiotics and for hypotensive drugs after operation. Three of these were young patients, aged 17, 14, and 13, so the risks are not limited to older patients. It is disappointing, for there were no deaths among the first 18 patients operated on from 1948–53.

Among the 45 deaths in the 648 resections reviewed, 35 seemed to be in cases without complications. The cause of death was given in 23 of these; in 9 it was hæmorrhage or cardiac arrest at or just after operation, in 10 late hæmorrhage from the suture line (infection being proved in four of these), in 2 cerebral hæmorrhage, in 1 cerebral damage, and in 1 mesenteric necrotizing arteritis. Intracranial hæmorrhage that was not fatal complicated three cases and paralysis of the legs three others. One late death from bacterial endocarditis has been recorded and aortic regurgitation has progressed in one boy of 15 in spite of a successful resection (O'Sullivan and Steinberg, 1953).

Results in this Series. In two early cases, no resection was possible but one of these may prove operable now that the use of grafts is more developed. In fact, grafts were used in 10 of the 46, but this is a higher proportion than usual.

Subsequent discussion is based on our first 30 patients who survived after resection. Four have been followed for from five to seven years, 9 for three or four years, 9 for two years, 6 for one year, and 2 for less than this. The blood pressure was always greatly reduced but not always to normal levels. The result during the first year was generally a reliable indication of the subsequent course and only in one patient has the pressure tended to rise during six years though not nearly to the original level. Only one patient failed to get a good result: his blood pressure fell but two months later rose to near the previous level and he then returned to Africa and has not been traced.

The final results will need a long follow-up for there must still be some risk of endocarditis on bicuspid aortic valves and of rupture of the aorta or of a berry aneurysm even if these are much reduced by the lower blood pressure. Berry aneurysms occur at sites of congenital weakness of the arterial wall and it is reasonable to expect that both their development and their rupture will be reduced by resection at an early age. The site of anastomosis and the graft itself, when this has been used, may not always remain satisfactory. So far, however, there have been no untoward episodes in these patients.

Sometimes the good result can be assessed by relief of symptoms but many patients felt so well and were so active that improvement in symptoms could not be expected. Several of them, however, felt better and some were obviously so. Two have returned to work that they had been forced to give up, and another is working much harder and yet is less aware of symptoms even though he had and has aortic regurgitation.

One example of an excellent result follows. A woman, aged 28, had been well till she was 25 but since then had found her work in a fruit shop as well as housework increasingly difficult because of headaches. Five years later she is doing these easily and looking after her small son, all without symptoms. Her blood pressure has fallen from 207/103 to 130/81 and her cardiogram is more normal. Her renal function tests, done two years after operation because there had been some albuminuria, were completely normal.

Changes in Blood Pressure. Apart from a long follow-up the success of the operation in safeguarding the patient's future can be judged best by the changes in the pressure. These are difficult to assess because of their variability but we have taken the average of many readings often over several years, and think that they give an accurate picture (Table V). Generally the systolic blood pressure stabilizes about 40 mm. lower and the diastolic about 20 mm. lower than it was, but there is, of course, great variation. One man still has a diastolic pressure of 101 mm. but as his systolic

TABLE V

LEVEL OF BLOOD PRESSURE BEFORE AND AFTER OPERATION FOR COARCTATION

	Before		After		Reduction	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
5 patients with the highest systolic pressures	207	115	148	90	59	25
Next 5 patients	197	109	144	87	53	22
Next 5 patients	185	112	142	87	43	25
Next 5 patients	173	104	143	84	30	20
Next 5 patients	162	102	127	78	35	24
5 children aged 3–13 with the lowest systolic pressures ..	146	88	117	75	29	13
Average of all patients ..	178	105	137	83	41	21

has fallen from 207 to 156 the result was counted as good. No other ptaient had a diastolic pressure over 95 mm. though two were at this level 6 and 4 years after. There were ten others where it was about 90 mm.

Most studies of patients after resection have reported the blood pressure as normal or reduced without much detail, though Hallenbeck *et al.* (1951) says that it was below 130/90 in 49 per cent, Gross (1953) says that it was below 140, with corresponding reductions for children, in 88 per cent, and Haxton and Milnes Walker (1954) report an average fall of 47/24 mm. in 25 cases. A more detailed study by Counihan (1956) finds that although the brachial blood pressure is much reduced it rarely falls to normal. By chance, the average pressure before operation was 178/105 in our series and 177/99 in his, but after it our figure was 137/83 against his 157/87. It is, of course, easy

to record the lower readings and neglect the higher ones, but we took them under the same conditions before and after operation, and they are about 10 mm. higher than the average figures obtained in the ward after the operation.

There has been a tendency to assume that when the pressure does not fall to normal, the surgeon has not relieved the obstruction completely, but Counihan doubts this and found no precise relationship between the fall of blood pressure and the apparent increase in the aortic diameter at the anastomosis.

Aortic Regurgitation. This was present in 8 of the 46 patients and did not seem to affect the result. At one time we thought aortic regurgitation a contra-indication but have come to look on it as an indication, for successful operation may delay its progress unless it is too far advanced. In one the diastolic murmur has become more difficult to hear.

The Size of the Heart after Operation. The heart is often of normal size and rarely very large, and those who have had operation have been within the usual range. In three of those who died, however, the heart was very large (c.t.r. 58–71%). In 21 of the 30 who survived with a completed resection it was not enlarged (c.t.r. 40–50) and remained just the same, and in 9 with larger hearts (c.t.r. 52–56%) the average cardiothoracic ratio fell from 53·4 to 52·4 per cent. Most of the larger hearts, however, were in adults where reduction in size—absolute as opposed to relative size in a growing child—must be hard to obtain and if obtainable must take time.

Electrocardiographic Changes. Of the 30 patients who had a completed resection, 11 had some left ventricular strain, generally no more than T waves that were flat or biphasic or slightly inverted in leads V5 and V6, and sometimes this was one of the reasons for advising operation. All these and another 14 had left ventricular preponderance, but 5 had not even this.

Generally the signs of left ventricular strain were lessened by successful operation, and in 6 they were almost or completely abolished (Fig. 10). Sometimes but less constantly the left ventricular preponderance also diminished.

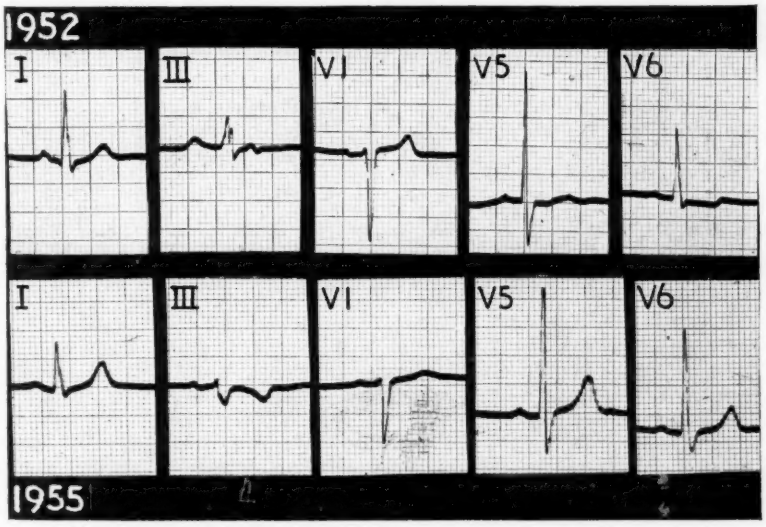

FIG. 10.—The disappearance of slight left ventricular strain after a successful operation. The slight S–T depression and small T waves in V5 and V6 have been replaced by large upright T waves. (A) Before operation when he was 18. (B) Three years after.

Summary and Conclusions

We have tried to summarize the progress of 130 patients with coarctation of the aorta, 80 of whom have been followed for an average period of five years. One-quarter of them have aortic regurgitation, generally from atherosclerotic changes on bicuspid valves, the percentage increasing as they get older. Generally the regurgitation remains slight for many years with the diastolic pressure still over 100, but becomes more serious as time goes on.

About 5 per cent have aortic stenosis, more often we think congenital than atherosclerotic. Patent ductus arteriosus was not common in our series and simple ventricular septal defect was not seen. Other congenital abnormalities are not common but occur.

Most patients get on well for the first two decades, though the blood pressure rises from an average of 145/90 at 5 years to 190/105 at 17 years of age or so, and then remains steady. The heart is often of normal size and rarely becomes very large unless there is free aortic regurgitation. Left ventricular preponderance is present in less than half the electrocardiograms and much left ventricular strain is rare in the absence of aortic stenosis, though slight degrees of this may suggest that a patient is not doing well.

In spite of the satisfactory progress of most patients, six who were in good health when they were first seen died suddenly or relatively so, most often in the third decade. We think, therefore, that most children should have surgical resection unless the evidence suggests the coarctation is trivial. Early aortic regurgitation is a further indication for it is likely to get worse unless arrested.

The results of surgical treatment are generally good. In our first 30 patients surviving with a completed resection all but one had much lower blood pressures and the average fall was 41 mm. for the systolic and 21 mm. for the diastolic pressure. Those who had disabling symptoms were much improved.

We are greatly indebted to Sir Russell Brock for asking us to see several of these patients, and still more for his work in making possible the last section on surgical treatment. We should like to thank Dr. Charles Baker and Dr. Ralph Kauntze for allowing us to include some of their patients: also Miss Waldron for Fig. 4, 7, and 8, and Mr. Engel of the Photographic Dept., Guy's Hospital, for the photographs.

One of us was Medical Registrar to Dr. John Fawcett for several years and does not remember that he ever mentioned coarctation though he had written an excellent paper on the subject in 1905: evidently he thought of it as a condition that was diagnosed at necropsy. It is interesting that 4 of his 18 cases had bicuspid valves ("two valves had coalesced") and 2 (including one with bicuspid values) had aortic stenosis.

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* The 648 resections that are reviewed are taken from these papers.

THE NAIL-FOLD CAPILLARIES IN COARCTATION OF THE AORTA

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While the role of the capillary in hypertension in man is not known, mainly owing to technical difficulties, Scheinker (1948), using histological methods, found that in arterial hypertension the early stages of cerebral vascular damage were confined to the capillaries which showed proliferative and degenerative changes. The existence of a hypertensive capillary pattern in the bulbar conjunctiva has been described by Lack *et al.* (1949). These capillary changes consisted of generalized narrowing of the lumen, elongation with angular tortuosities, abnormal coiling, looping, and occasionally sacculations, and their severity could be directly correlated with the height of the diastolic blood pressure. Lee and Holze (1951) found similar capillary changes in the bulbar conjunctiva of hypertensive patients. In spite of these findings, Goldblatt (1951) stated that it had been impossible to arrive at any conclusion about the causative relationship between the changes in the capillaries and hypertension.

The capillaries of the finger nail-fold of patients with hypertension were observed by Boas (1921) to have a greatly accelerated rate of blood flow. Brown and Roth (1927) found no characteristic morphology in essential hypertension although there was an increased tortuosity of the loops as compared with the normal for the age group: rapid alternation of fast and slow rates of blood flow were observed frequently. Weiss and Frazier (1930) noted irregularity of the loops and the frequent occurrence of a narrowed, hair-like arterial limb. Wright and Duryee (1933) stated that while much increase of blood pressure was often associated with an increased tortuosity of the nail-fold capillaries, there were many exceptions to the rule. Greisman (1954) noted that the rate of blood flow was usually rapid in essential hypertension and in hypertension induced by lævonoradrenaline administration.

Lombard (1912) was the first to observe the capillaries of the living nail-fold. If oil be placed on the skin of the nail-fold and it be examined under a microscope, hair-pin shaped capillary loops are seen lying parallel to the skin surface. These loops are arranged in palisades of which there may be two, three, or four. The capillaries appear bright red against a background of pink, and the arterial limb of the loop is narrower than the venous limb. The identity of the limbs can be established by observation of the direction of blood flow within them. The rate of blood flow may be observed but its measurement is difficult. It is almost always possible to obtain a clear view of the capillary loops and dimly to see the sub-papillary plexuses.

The appearance of these capillaries even in normal persons is subject to wide variation. Roth (1946) stated that it had been impossible to establish a single standard type of normal nail-fold capillary. The appearance of the capillaries changes with age. Mayer (1921) in a study of the capillaries of the new-born, found an irregular branching network close to the skin surface. By the age of six months, the adult pattern of capillary loops was usually established, and an increased length and incidence of tortuous loops with advancing age was found by Roth (1946).

While the capillaries of the nail-fold of the toes have not been studied as intensively as those of the fingers, they have a similar morphological pattern. The skin tends to be thicker over the toes, thus hindering observation. In my experience, the capillaries of the toes are usually considerably smaller than those of the fingers.

It is difficult to know what capillary changes to ascribe to disease when the normal pattern of the capillaries can vary so much from one person to another.

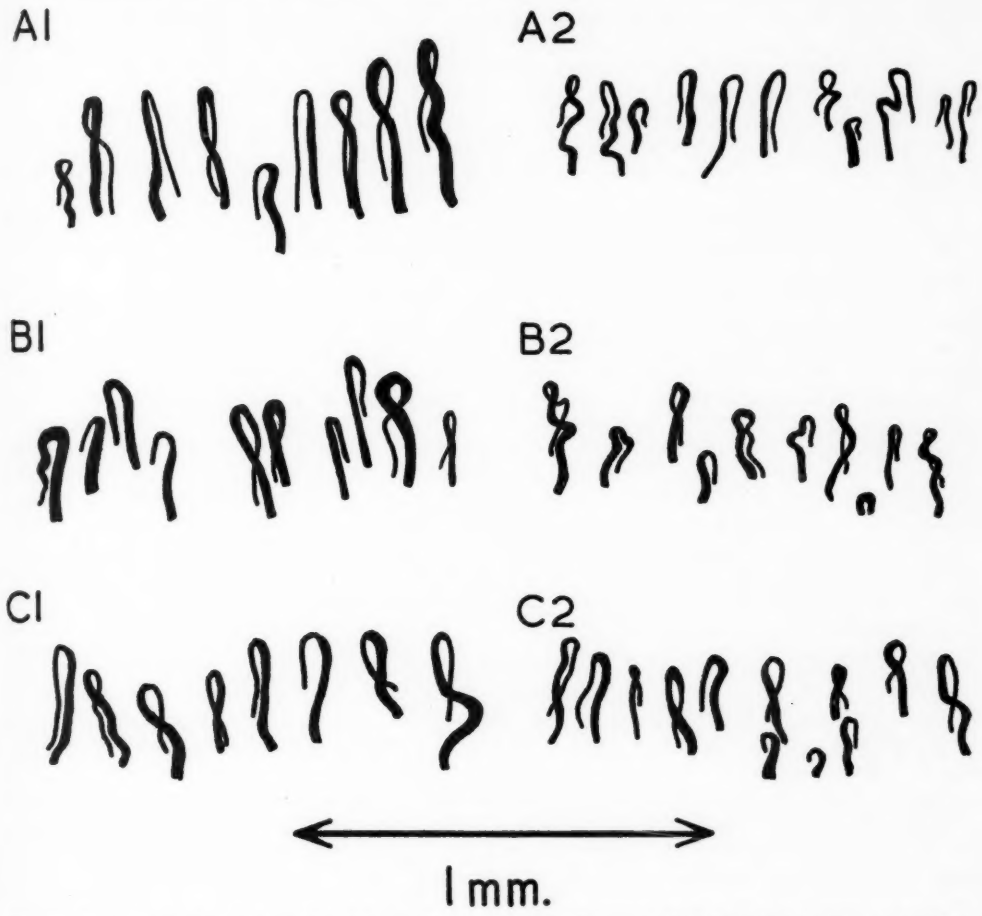

FIG. 1.—Tracings of microphotographs of the capillary loops of the fingers on the left, and of the toes, on the right. (A) In a normal subject. (B) In Case 1; and (C) in Case 2.

OBJECT AND METHOD OF THIS STUDY

The present study was undertaken to determine whether there was a significant difference between the appearance of the nail-fold capillaries in the fingers and the toes of patients with coarctation of the aorta. In this congenital malformation, the blood pressure is increased in the upper part of the body and decreased in the lower part. This condition affords the opportunity of studying the periphery of an arterial tree, subjected to a wide difference in blood pressure, in separate sites, within the same individual. It therefore seemed to be appropriate to find out whether there was a variation in the degree of tortuosity of the capillaries in the upper and lower limbs in a series of patients with coarctation of the aorta.

Method. A Watson Service microscope had a sheet of metal incorporated into the movable stage, and upon it plasticine was moulded. The digit to be examined was introduced into a groove made in the plasticine, which was then gently pressed around to provide a degree of fixation compatible with integrity of the circulation. A drop of glycerin was placed over the nail-fold and a coverslip balanced upon it to reduce the surface reflection of light. The illumination was provided by a powerful tungsten filament lamp in an Edison lamphouse. With a 1·5-in. objective glass and a ×10 eyepiece magnification of about forty diameters was obtained. With this optical arrangement a wide area could be studied and the overall pattern of the capillaries observed. For a more detailed study of individual capillaries, and for assessment of the rate of blood flow, a 16-mm. objective glass was used in conjunction with the same eyepiece, giving an approximate magnification of a hundred diameters.

For microphotography, a 35-mm. eyepiece camera was used in conjunction with an electronic flash of a hundred Joules output. This apparatus gave an effective exposure of about one-thousandth of a second.

Material. The capillaries of the finger and toe nail-fold were examined in fifteen normal subjects and in four patients with coarctation of the aorta. The patients with coarctation were males of 10, 17, 21, and 35 years. The subjects of the control series were of similar ages. Each patient with aortic coarctation had brachial hypertension and none had a recordable blood pressure in the legs. All had arterial collateral circulation. In one patient who died after operation aortic coarctation was confirmed at autopsy.

Results

Microphotographs of the finger and toe nail-fold capillaries of each of the patients with coarctation of the aorta were taken and tracings from these are shown together with those of one normal subject. These illustrations are taken as confirming the finding on direct observation, that in no case of aortic coarctation did the degree of tortuosity of the finger capillaries exceed that of the toes. The rate and nature of blood flow, as judged by direct observation, seemed to be identical. The toe capillaries in coarctation of the aorta were smaller than the finger capillaries but not by an amount more than that seen in the control series.

Summary and Conclusions

The capillaries of the nail-fold of fingers and toes were examined in four patients with coarctation of the aorta and in fifteen normal subjects. In the two groups examined, no significant differences were found.

Elevation of the blood pressure alone does not, therefore, cause any change in the morphology of the cutaneous capillaries of the nail-fold of the fingers.

No information of value in diagnosis is to be obtained from examination of the nail-fold of the fingers and toes in patients with coarctation of the aorta.

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TRICUSPID ATRESIA

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Tricuspid atresia is an uncommon form of cardiovascular malformation which occurred as the primary lesion 16 times in Abbott's (1936) 1000 cases of congenital heart disease and in 5 per cent of 670 of Campbell's (1953) patients with cyanotic congenital heart disease. Although isolated cases, such as Hedinger's (1915) patient who was 56, have been described in adult life, most of the patients with this rare anomaly have been reported in infancy or early childhood: 9 of the 15 cases of Astley *et al.* (1953) were 2 years of age or under and the oldest was 11 years. The features of 8 patients with tricuspid atresia, 7 of whom were 3 years or over, and of one patient with congenital tricuspid stenosis, aged 13, are described in the present communication, where the clinical manifestations of the disease in older patients and its diagnosis by special investigation are discussed. In four of the patients who died (Cases 2, 3, 5, and 8) an account is given of the pathological findings which are considered in relation to survival. In two of these (Cases 2 and 8) a histological examination of the small pulmonary vessels was made and the abnormal appearances found in Case 2 are described.

Clinical Features

Symptomatology. All 9 patients complained of breathlessness on exertion and, with the exception of Cases 4 and 8, had suffered from frequent coughs and colds. Cyanosis had been noted from birth in all except Case 9. On exertion Cases 1 and 2 had chest pain and Cases 1 and 7 had dizziness. Only Cases 5 and 9 had squatted. Cases 1 and 6 complained of palpitation.

Signs. All the patients except Case 9 showed gross central cyanosis and finger clubbing. In Case 9 the central cyanosis and finger clubbing were slight. Apart from Case 1, where the apex beat was felt in the fifth left intercostal space in the anterior axillary line, there was no clinical evidence of cardiomegaly. On auscultation none of the patients had a diastolic murmur or clinical evidence of pulmonary hypertension. The other clinical features are shown in Table I.

Electrocardiography. Electrocardiograms were recorded in all except Case 8 in the present series. All the tracings showed left axis deviation and in Cases 2, 3, 5, 6, and 7 there was also evidence of clockwise rotation of the heart (Fig. 1 and 2). There were abnormally tall peaked P waves in lead II, taking the upper limit of normal to be 2·5 mm. (Goldberger, 1953) in Cases 2 and 3, and using the criteria of Sokolow and Lyon (1949), there are cardiographic evidences of left ventricular hypertrophy in Cases 1 and 2.

Radiological Examination. The radiological findings in this series were summarized in Table II; the postero-anterior teleradiograms of Cases 1, 3, 4, and 5 are reproduced in Fig. 3 and the left anterior oblique views of Cases 2 and 5 in Fig. 4.

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TABLE I

FEATURES OF NINE PATIENTS WITH TRICUSPID ATRESIA

Case	Age	Sex	Systemic blood pressure in arms (mm. Hg)	Ausculatory signs		Character of cardiac impulse	Prominent wave in jugular venous pulse	Hæmoglobin in grams per 100 ml.
				Mitral area	Pulmonary area			
1	44	F	100/60	SM	SM P2 loud and single	Apical thrust	Systolic	16·1
2	7	M	105/85	SM	SM P2 inaudible	Heave over lower sternum	Presystolic	20·4
3	6	M	—	SM	SM * P2 loud and single	—	Presystolic	19·2
4	13	M	120/80	SM	SM * P2 loud and just split	Apical thrust	Presystolic	20·0
5†	13	F	100/75	SM	SM P2 single	Heave over lower sternum	Presystolic	18·5
6†	3	F	—	—	P2 loud and just split	—	—	13·0
7	3	F	—	SM	SM * P2 soft and just split	Heave over lower sternum	—	16·1
8†	3 mo.	F	—	SM	SM	—	—	—
9	6	M	115/80	SM	SM P2 single	Not diagnostic	Presystolic	16·1

* Associated thrill.

† Case 5 was a mongol, Case 6 had a cleft palate, and Case 8 had congestive heart failure.

SM=Systolic murmur. The murmur was maximal at the base in all except Case 7 where it was maximal at the mitral area.

Angiocardiography. An angiocardiographic examination was carried out in 8 patients in the present series. In all except Case 5 the contrast medium passed within three seconds of injection from right to left atrium through an atrial septal defect and into the left ventricle (Fig. 5 and 6). These chambers appeared larger than normal. Left atrial filling was well seen in the lateral view within two seconds of injection. Although in Case 5 there was no early filling of the left atrium, the left ventricle was fully opacified in two seconds (Fig. 6) and even in the later films there was only slight opacification of the left atrium. These anomalous findings were explained by examination of the heart at necropsy and are further considered in the discussion. There was a characteristic clear area, called the " right ventricular window " by Campbell and Hills (1950), between the contrast medium in the right atrium and the left ventricle in all except Case 5. A small right ventricle opacified in this clear area except in Case 4 and this appeared to fill from the left ventricle (Fig. 5). The lateral angiocardiograms showed evidence of transposition in Case 4.

Cardiac Catheterization. This investigation was carried out in Cases 3 and 9. The catheter passed from the right atrium through an atrial septal defect into the left atrium. From this position the tip was directed into the left ventricle and the right and left pulmonary veins (Fig. 7). Blood samples for blood oxygen estimation were taken from the various sites entered by the tip of the catheter and intracardiac blood pressures were recorded (Fig. 8). In Case 3 the tip of the catheter

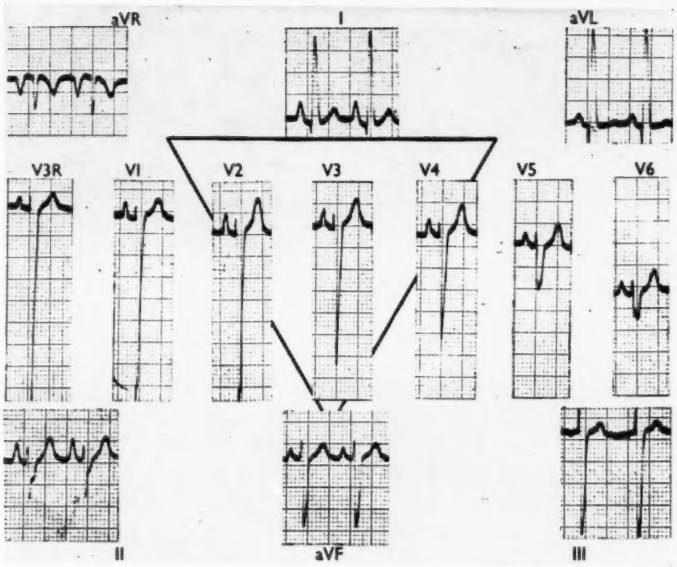

FIG. 1.—Electrocardiogram showing left axis deviation and peaked P waves. Case 3.

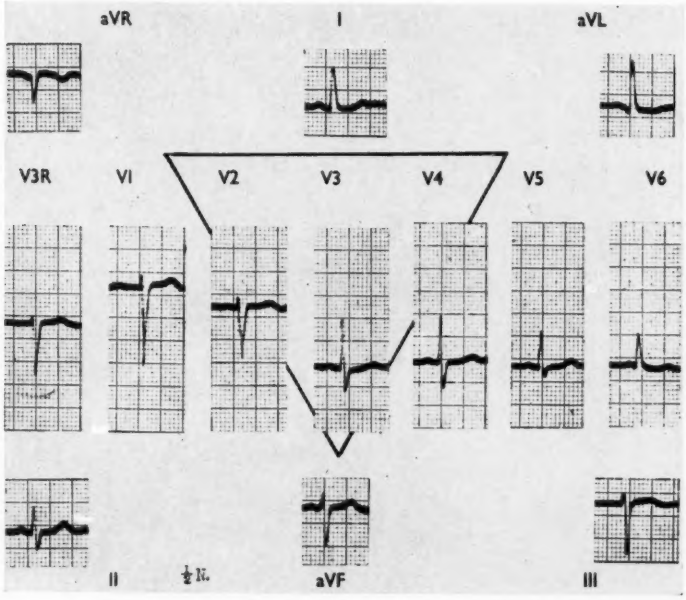

FIG. 2.—Electrocardiogram showing left axis deviation without peaked P waves. Case 4.

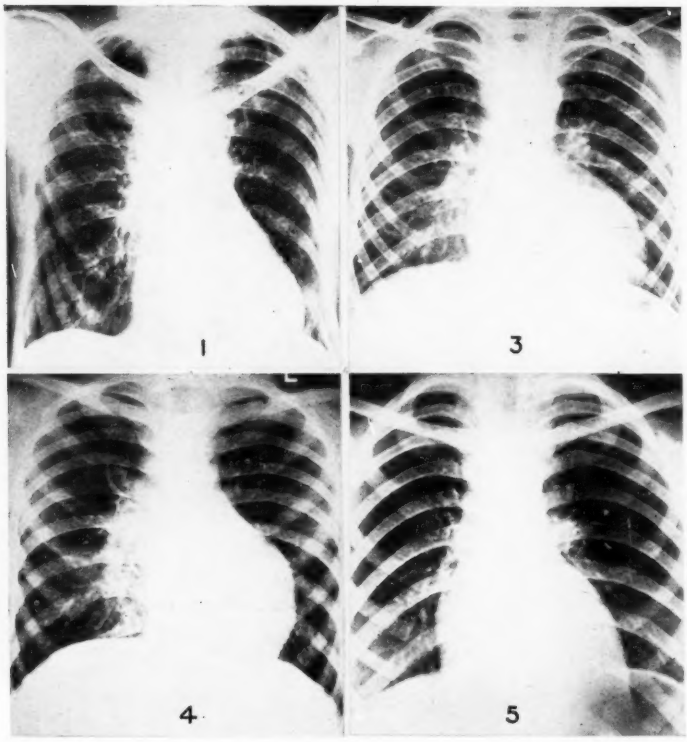

FIG. 3.—Postero-anterior teleradiograms of three patients with tricuspid atresia (Cases 1, 3, and 4) and one with congenital tricuspid stenosis. Case 5.

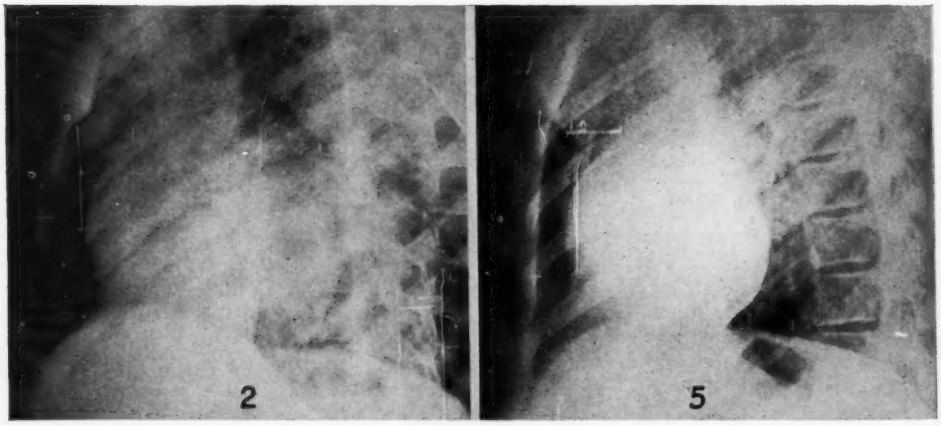

FIG. 4.—Left anterior oblique radiograms in Cases 2 and 5. Case 2 shows abnormal prominence of the posterior border, including the upper part, due to enlargement of the left ventricle and atrium, confirmed at autopsy. Case 5 shows no abnormal prominence of the posterior border although at autopsy the left ventricle was found to be large in this patient also.

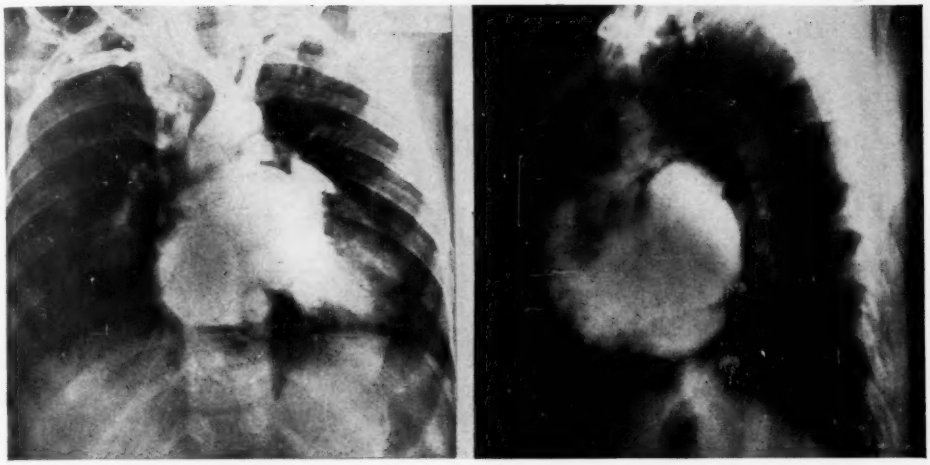

FIG. 5.—Postero-anterior and lateral angiograms at 2 seconds. The postero-anterior film shows early filling of the left atrium and a " ventricular window " with a diminutive right ventricle. The lateral film shows early filling of the left atrium and a normal origin of the great vessels. Case 2.

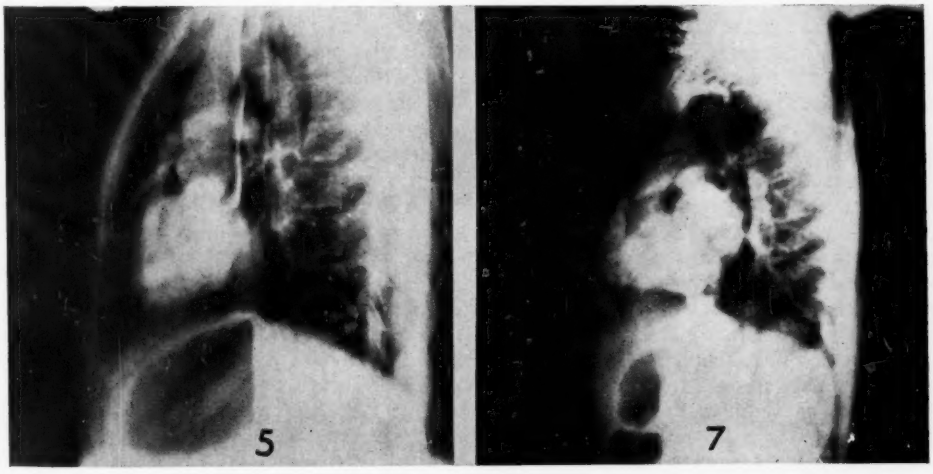

FIG. 6.—Lateral angiograms at 3 seconds. Case 7 shows early filling of the left atrium with contrast medium, whereas Case 5 does not. Hypoplasia of the pulmonary artery is well seen in Case 5.

TABLE II

RADIOLOGICAL FINDINGS IN 8 PATIENTS WITH TRICUSPID ATRESIA

	Postero-anterior view						Left anterior oblique view		
Case No.	Overall cardiac enlargement	Shape	Concavity of left middle segment	Prominence of main branches of pulmonary artery	Peripheral pulmonary vascularity	Prominence of right border of heart	Abnormal prominence of left auricular curve	Abnormal prominence of left ventricle	Anterior border
1	S	Triangular	+	N	I	N	—	—	C
2	S	Square	+	N	D	F	+	+	C
3	S	Boot	+	N	D	F	...	+	...
4	S	Square	+	I	I	D	—	—	F
5	S	Bottle	+	D	D	N	—	—	C
6	S	Normal	+	D	N	D	+	+	C
7	S	Boot	+	I	I	F	+	+	F
9	O	Triangular	—	N	D	F	+	+	C

Key: S=slight. O=none. ... =no observation made. N=normal. I=increased. D=diminished. F=flat. C=convex. +=present. —=absent.

was re-inserted into the left upper pulmonary vein and contrast medium was injected which outlined the vessel (Fig. 7). The arterial blood oxygen saturation was measured in Case 1 and was 37 per cent.

NECROPSY FINDINGS

Necropsy examinations were carried out in Cases 2, 3, and 5 who died following anastomotic operations and in Case 8 who died with congestive cardiac failure.

Case 2. On opening the chest there were numerous anastomotic channels over the pericardium and mediastinal pleura. Only the left ventricle was visible judging by the extreme right-sided position of the anterior descending branch of the left coronary artery. On dissection of the heart the right atrium was dilated with a large right atrial appendage (Fig. 9). Its wall was 2 mm. thick. There were four defects in the atrial septum, a large defect 10 mm. in diameter in the region of the foramen ovale and three small defects immediately below this (Fig. 10). The left atrium was dilated and the mitral ring was wide. The left ventricle was dilated and hypertrophied, its wall being 15 mm. thick 10 mm. below the attachment of the mitral valve, which was normal in structure. The aorta was dilated but the aortic valve was normal; the aorta and pulmonary artery arose in their normal position. There was a diminutive right ventricle lying slit-like in the right wall of the left ventricle; its free wall was 2 mm. thick and its cavity 15 mm. long. There was a muscular ventricular septal defect. There was atresia of the tricuspid valve. The pulmonary artery was hypoplastic and the pulmonary valve had three delicate semilunar cusps. There was no atheroma of the pulmonary vascular tree. The ductus was obliterated.

Histology of the Small Pulmonary Vessels (*Fig. 13*). The elastic pulmonary arteries (>1000μ) were normal. There was no medial necrosis or atheroma. The vasa vasorum in the adventitia of these vessels were normal. The muscular pulmonary arteries (100–1000μ) were thin-walled and there was widespread thrombosis in these vessels throughout the lungs. They were filled with organizing thrombi which had disorganized the structure of the vessels so that it was difficult to

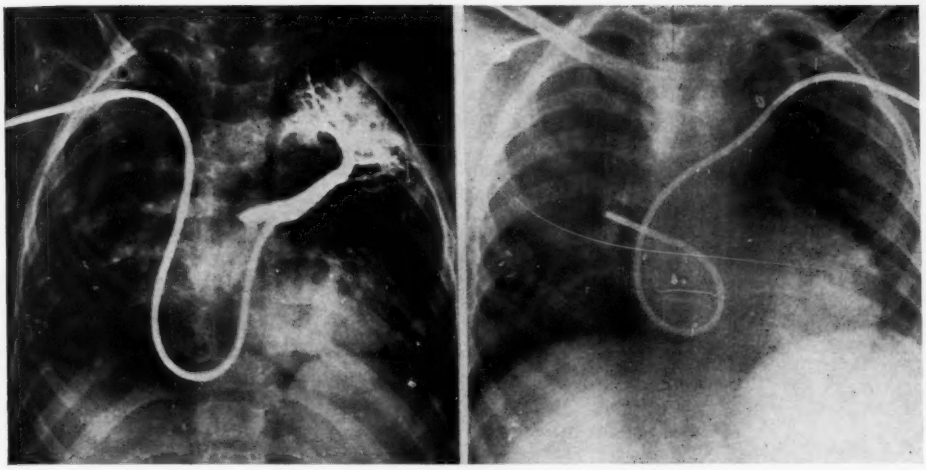

FIG. 7.—Films taken at cardiac catheterization. On the left the cardiac catheter has been passed through an atrial septal defect into a left upper pulmonary vein and contrast medium has been injected to outline the tributaries of this vein. On the right the cardiac catheter has been passed through an atrial septal defect into the right upper pulmonary vein. Case 3.

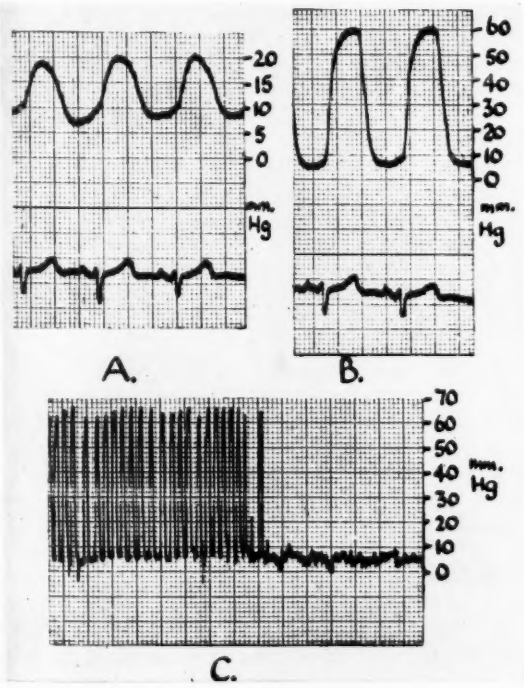

FIG. 8.—Blood pressure tracings taken at cardiac catheterization with the tip of the catheter in the right atrium (A), in the left ventricle (B), and being withdrawn from the left ventricle to the left atrium (C). Case 9.

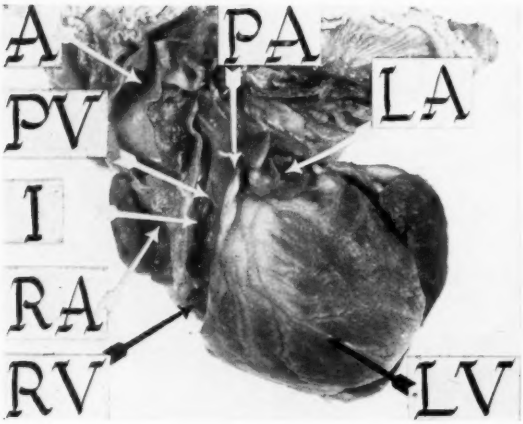

FIG. 9.—The heart has been dissected to show the small right ventricle lying in the wall of the hypertrophied left ventricle. Case 2.
RA=Right atrium. PV=Pulmonary valve. LA=Left atrium. PA=Pulmonary artery. RV=Right ventricle. I=Infundibulum. LV=Left ventricle. A=Aorta.

FIG. 10.—The left atrium and the left ventricle have been opened to show the wide mitral ring and the patent foramen ovale. Case 2.
LA=Left atrium. MV=Mitral valve. LV=Left ventricle. ASD=Atrial septal defect.

distinguish between arteries and veins. The pulmonary arterioles were thin-walled and showed extensive intravascular thrombosis. The visceral pleura was vascular, the layer of vascularity being about 300μ in depth and consisting of thin-walled vessels enmeshed by strands of fibrous tissue and elastic fibrils. Most of these vessels were $90 \times 30\mu$ in diameter. There was no smooth muscle in the pleura. The lung parenchyma was unduly vascular, the increased vascularity being due to numerous dilated thin-walled vessels. Some of these were large, measuring about $600 \times 200\mu$, but even the capillaries were dilated. On serial section, communications were demonstrated between the dilated vessels in the lung parenchyma and those in the vascular layer in the pleura but no anastomoses were shown between the vasa vasorum of the elastic arteries and the vessels of the lung parenchyma. The muscular pulmonary arteries gave off large dilated thin-walled branches. The intravascular thrombi were in various stages of organization and in most vessels there was multiple recanalization of old thrombus which gave a striking angiomatous appearance throughout the lung (Fig. 13). This appearance was produced by recanalization of thrombus and was not due to thin-walled collections of vessels such as are found in the lung in conditions producing bronchopulmonary anastomoses.

Case 3. The right atrium was large and in free communication with a dilated left atrium by means of an atrial septal defect 30 mm. in diameter which occupied the upper half of the atrial septum. The left ventricle was dilated and hypertrophied, its wall being 14 mm. thick just below the mitral valve, which was normal in structure. The mitral ring was dilated. The aorta was dilated with a normal aortic valve. There was no transposition of the great vessels. There was a diminutive right ventricle lying slit-like in the right wall of the left ventricle; its free wall 3 mm. thick, its cavity 25 mm. long. There was atresia of the tricuspid valve and there was a muscular ventricular septal defect.

Case 5. On superficial examination of the heart there appeared to be only a single ventricle, but on dissection a small right ventricle was found buried in the right wall of the dilated and hypertrophied left ventricle (Fig. 11). The cavity of the right ventricle was 50 mm. long and the free wall of this chamber only 3 mm. thick. The thickness of the left ventricular wall at the level of the insertion of the mitral valve was 10 mm. The great vessels arose normally from the ventricles,

the pulmonary artery was hypoplastic and free of atheromatous deposits. The pulmonary valve had three delicate semilunar cusps. There was a patent ductus arteriosus, 20 mm. long and 10 mm. in diameter. The right atrium was very large (Fig. 11) and since there was a persistent ostium primum it communicated freely with the hypertrophied left ventricle. The left atrium was small and received the pulmonary veins. There were three defects in the atrial septum the dimensions of which were 8×5 mm., 10×8 mm., and 4×3 mm. There was a small muscular ventricular septal defect (Fig. 12). There was stenosis of the tricuspid valve. The aorta was dilated but had three normal semilunar cusps. The free communication between the right atrium and the left ventricle due to the persistent ostium primum and the small atrial septal defects allowed blood to pass directly from the right atrium to the left ventricle rather than to the left atrium (Fig. 11). Since the persistent foramen primum provided a free communication from right atrium to left ventricle, the main flow of blood was probably in this direction rather than through the small atrial septal defect into the left atrium.

Case 8. The right atrium was enormous and its capacity appeared as great as the rest of the heart together. Its wall was 3 mm. thick, and it communicated with a dilated left atrium through an atrial septal defect 30×20 mm. in size. The left ventricle was dilated and its wall was 12 mm.

FIG. 11.—The left ventricle has been opened and the stenosed tricuspid orifice leading to a diminutive right ventricle has been marked by a rectangular white marker. The upper large white arrow indicates the direction of blood flow from the S.V.C. to the large right atrium and thence via a patent foramen primum into the left ventricle. The lower large white arrow indicates the direction of blood flow from the left atrium to the left ventricle. Two of the defects in the atrial septum in the region of the patent foramen ovale can be seen. Case 5.
SVC=Superior vena cava. PFO=Patent foramen ovale. TS=Tricuspid stenosis. PFP=Patent foramen primum. LV=Left ventricle. RA=Right atrium. MV=Mitral valve.

FIG. 12.—Heart dissected to show small right ventricle lying in the wall of the hypertrophied left ventricle. A grey indicator in the right ventricle shows the site of a muscular ventricular septal defect. A white indicator has been passed through a patent ductus arteriosus from the pulmonary artery into the aorta and a third through the superior vena cava. Case 5.
VSD=Ventricular septal defect. RV=Right ventricle. I=Infundibulum. PV=Pulmonary valve.

thick 1 mm. below the mitral valve. It communicated with a small thin-walled (3 mm.) right ventricle by means of a membranous ventricular septal defect 5 mm. in diameter. There was no transposition of the great vessels. The aortic, pulmonary, and mitral valves were normal.

Discussion

Symptomatology. There is no symptom that is specific or even particularly suggestive of tricuspid atresia and the usual presenting triad of central cyanosis, dyspnœa on exertion, and frequent chest infections is common to most forms of cyanotic congenital heart disease. Central cyanosis which is present from birth or infancy is usually gross. Case 9 in the present series was not considered abnormally blue by his parents and had only a slight degree of central cyanosis, but in the other patients the cyanosis was easily discernable. Exceptionally, cyanosis may be absent: Gasul *et al.* (1950) reported an acyanotic case of tricuspid atresia where death occurred at the age of five months, but it is probable that central cyanosis would have developed had this child lived longer. Dyspnœa on exertion occurred in all the present patients and has been described with great frequency in previous reports (Rogers *et al.*, 1950; Kroop, 1951; Astley *et al.*, 1953; and Edwards *et al.*, 1954). Frequent coughs and colds, which occurred in 8 of our patients, have not been commonly described.

Other symptoms that occur in association with tricuspid atresia appear so infrequently as to be of little diagnostic importance. Cases 1 and 7 in the present series suffered from dizziness on exertion but none had the spontaneous attacks of unconsciousness reported by Astley *et al.* (1953).

Squatting, which is not a common feature of tricuspid atresia, occurred in only two of the present series, Cases 5 and 9, and one of the 15 cases reported by Astley *et al.* (1953).

Signs. Central cyanosis and a præcordial systolic murmur without evidence of associated pulmonary hypertension are the dominant signs of tricuspid atresia. These features are exceptionally constant and have been noted by Taussig (1947), Brown (1950), Sommers and Johnson (1951), Kroop (1951), Anderson and McKee (1952), Astley *et al.* (1953), Edwards *et al.* (1954), Edwards (1953), and Kaplan and Robinson (1954). However, they are not diagnostic of the anomaly since they occur in other forms of cyanotic congenital heart disease such as Fallot's tetralogy, Ebstein's disease, and pulmonary stenosis with reversal of flow through a septal defect.

In congenital tricuspid atresia and stenosis, systemic venous blood mixes with pulmonary venous blood either by passing through an atrial septal defect into the left atrium or directly into the left ventricle (Case 5). In either instance there is a complete admixture of systemic and pulmonary venous blood causing left ventricular and systemic arterial blood to be unsaturated with oxygen. The degree of arterial oxygen unsaturation varies from case to case according to the amount of blood passing to the lungs. The central cyanosis that is observed clinically depends upon the degree of oxygen unsaturation and polycythæmia. Where cyanosis is absent, as in the case reported by Gasul *et al.* (1950), or develops in infancy, as in the cases reported by Dustin-Henry and Dustin (1947) and Astley *et al.* (1953), it is unlikely that the arterial blood is ever fully saturated with oxygen and the late appearance of the cyanosis is most probably determined by the development of polycythæmia. In the present series all except Cases 6 and 8 had abnormally high hæmoglobin values (Table I).

Finger clubbing, which is usually associated with severe degrees of cyanotic congenital heart disease, was present in all our patients and is to be expected when a case of tricuspid atresia survives infancy (Rogers *et al.*, 1950; Brown, 1950; Anderson and McKee, 1952; Astley *et al.*, 1953; and Edwards, 1954).

The systolic murmur in tricuspid atresia is usually maximal over the base of the heart and may be accompanied by a thrill (Table I). It is usually heard better to the left of the sternum but may be maximal in the second right intercostal space or even in the mitral area as in Case 7 where it was accompanied by a thrill. The murmurs accompanied by thrills in the present series radiated widely over the whole chest and into the neck. No particular diagnostic significance was attached

to this radiation which was most probably determined by the intensity of the murmur. In Case 6 and in a case reported by Rogers *et al.* (1950) no murmur was heard. Kroop (1951) noted a diastolic murmur in the pulmonary area as well as a systolic murmur. Taussig (1947) considered that the murmur in tricuspid atresia originated from the passage of blood through the atrial septal defect or through an associated patent ductus arteriosus while Brown (1950) pointed out that a ventricular septal defect might be responsible. Another possible cause of the systolic murmur is the blood flow through collateral bronchial blood vessels which may be found in association with tricuspid atresia (Cases 1 and 2). The passage of blood through such vessels may have been the cause of the diastolic murmur noted by Kroop (1951).

The presence of an abnormally prominent venous pulse in 6 of our patients is in accord with the observations of Astley *et al.* (1953) who agreed with Taussig (1947) that in infants with tricuspid atresia this abnormal venous pulsation was most easily detected on palpation of the liver. In the jugular veins the abnormal pulse appeared clinically presystolic in 5 patients in this series and systolic in the other (Table I). A jugular phlebogram confirmed a single systolic venous wave in Case 1 but in Case 3 demonstrated that the abnormal wave which had been interpreted clinically as a giant " a " wave was an " ac " wave (Fig. 14). Taussig (1947) suggested that the abnormally prominent jugular venous pulse in tricuspid atresia was due to vigorous contractions of the right atrium attempting to expel blood through a small atrial septal defect into the left atrium. Prominent systolic venous waves may be caused by regurgitation of blood from the left ventricle into

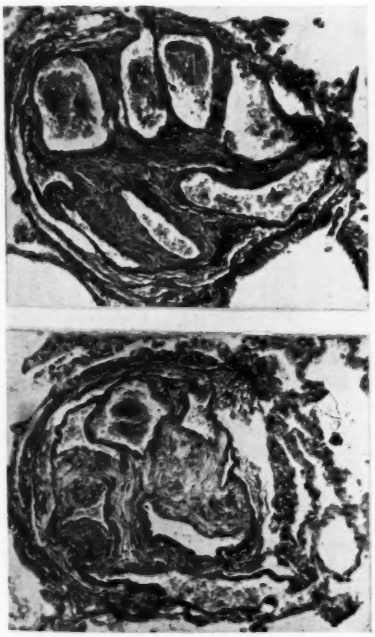

FIG. 13.—Transverse sections of two small pulmonary vessels, showing organized thrombus with multiple recanalization. It is impossible to identify these vessels as muscular pulmonary arteries or pulmonary veins. Verhœff/van Gieson stain. Magnification, ×180. Case 2.

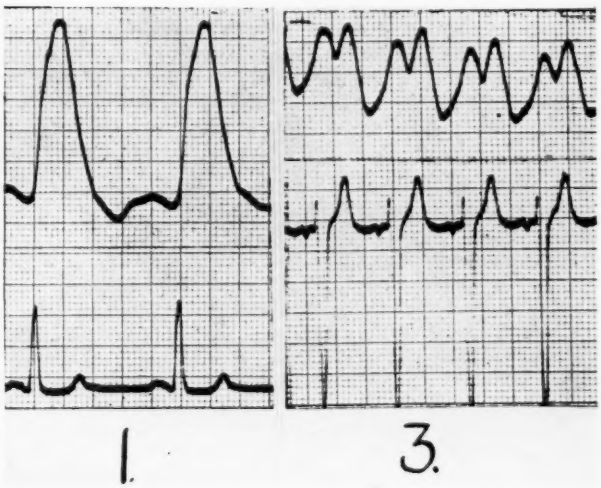

FIG. 14.—Synchronous records of the jugular phlebogram and the electrocardiogram. Case 1 shows single systolic venous waves. Case 3 shows *ac* and *v* waves.

the right atrium through a wide mitral ring and a large atrial septal defect. The variety of jugular venous pulsations in the present patients suggests that there is no abnormal pulsation diagnostic of tricuspid atresia. The presence of an abnormal presystolic pulsation is not of great diagnostic value since giant " a " waves commonly occur in patients with other forms of congenital heart disease associated with either pulmonary hypertension or pulmonary stenosis.

Electrocardiography. Left axis deviation in the electrocardiogram is a characteristic but not pathognomonic feature of tricuspid atresia (Fig. 1 and 2). In a patient with cyanotic congenital heart disease this electrocardiographic sign suggests tricuspid atresia as the probable diagnosis. Left axis deviation was present in all the patients in this series but it is not invariably found in this anomaly and was absent in 2 of the 6 cases reported by Kroop and Grishman (1950) and 1 of the 15 cases reported by Kreutzer *et al.* (1954). A minor degree of right axis deviation was noted by Astley *et al.* (1953) in 1 of their 15 patients with tricuspid atresia. Left axis deviation occurs in other forms of cyanotic heart disease, such as persistent truncus arteriosus and common ventricle (Brown, 1950), complete transposition of the great vessels (Astley *et al.*, 1953), congenital aortic atresia (Soloff, 1949), and infantile coarctation with cyanosis (Donzelot *et al.*, 1950). It rarely occurs in Eisenmenger's complex (Astley *et al.*, 1953; Bond, 1951; and Brown *et al.*, 1955) and was noted by Astley *et al.* (1953) in a child with cyanosis due to methæmoglobinæmia.

Tall, peaked P waves were regarded as a characteristic feature of tricuspid atresia by Kreutzer *et al.* (1954) and by Kroop and Grishman (1950). Although these authors thought that the P waves were peaked in all their cases they did not specify the height of the P waves which they considered to be abnormal. In the present series only two patients having P waves more than 2·5 mm. in lead II were considered to show abnormally peaked P waves according to the criteria defined by Goldberger (1953) (Fig. 1). This suggests that abnormally tall P waves are not such a common feature of tricuspid atresia as had been suggested by the previous authors and since peaked P waves occur in other forms of cyanotic congenital heart disease such as Fallot's tetralogy, pulmonary stenosis and atresia, transposition of the great vessels, and Ebstein's disease they cannot be regarded of great diagnostic importance in tricuspid atresia. When they are present in tricuspid atresia they are probably due to hypertrophy of the right atrium, as in the other conditions. There was no heart block in cardiograms of the present patients but Astley *et al.* (1953) reported left bundle-branch block in one of their 15 patients and Dickson and Jones (1948) reported a case showing complete heart block.

Radiology

Astley *et al.* (1953) made a critical review of the radiological features of tricuspid atresia and concluded that it was often possible to diagnose the lesion from radiological examination. In the frontal projection a square-shaped heart, produced by concavity of the pulmonary segment and prominence of the upper part of the left lower segment below which the left cardiac border is vertical, was considered the most striking radiological feature. They thought that left ventricular hypertrophy might affect the upper part of the left lower segment of the cardiac border, but believed, from angiocardiographic evidence, that accentuation of this segment in patients with tricuspid atresia was due to prominence of the left atrial appendage. Four of the present patients showed a left atrial appendage on angiocardiography but only in Case 4 did it contribute to the square-shaped heart seen in the frontal projection (Fig. 3). Astley *et al.* (1953) pointed out also that this square-shaped configuration of the heart was rarely seen in Fallot's tetralogy, which is of great interest, since other authors have stressed the similarity of the radiological features of tricuspid atresia and the tetralogy of Fallot. Wittenborg *et al.* (1951) considered that 9 of their 11 patients with tricuspid atresia had a " cœur en sabot " resembling that of Fallot's tetralogy. Marder *et al.* (1953) stated that the cardiac silhouette in tricuspid atresia was rarely distinguishable from that of Fallot's tetralogy, while Soulié (1952) also commented on the similarity of the two conditions. Abrams and Alway (1951) thought that elevation of the cardiac apex was less striking with tricuspid atresia than with Fallot's tetralogy.

When the shape of the heart was examined in the frontal projection in the present series, none had more than a slight degree of cardiac enlargement; two, Cases 2 and 4, had square-shaped hearts; two, Cases 3 and 7, had a " cœur en sabot "; two, Cases 1 and 9, had triangular-shaped hearts; one, Case 6, had a

normal shaped heart, and in Case 5, with congenital tricuspid stenosis, the heart was bottle-shaped (Fig. 3, Table II). Since only 2 of the 9 patients in the present series and only 6 out of 15 reported by Astley *et al.* (1953) had square-shaped hearts the diagnostic importance of this feature should not be over-emphasized. When present, such a configuration is strongly suggestive of tricuspid atresia, but many patients with this lesion will have hearts of other shapes that are not diagnostic and probably indistinguishable from Fallot's tetralogy.

Concavity of the left middle segment of the cardiac border, which Astley *et al.* (1953) noted as a contributing feature to a square-shaped heart, has in itself been described as a characteristic feature of tricuspid atresia by Taussig (1947), Brown (1950), Rogers *et al.* (1950), Abrams and Alway (1951), Schnitker (1952) and Soulié (1952). Taussig (1947) considered that the concavity in the pulmonary segment was due to absence of the right ventricle but noted that it occurred in some cases of Fallot's tetralogy, transposition of the great vessels, and truncus arteriosus as well as tricuspid atresia. Although a concave pulmonary segment was observed in all except Case 9 in the present series (Fig. 3, Table II) this feature is not regarded as specifically diagnostic of tricuspid atresia but as a sign of hypoplasia of the right ventricle. Marder *et al.* (1953) stated that in patients with tricuspid atresia with transposition of the great vessels without pulmonary stenosis, the pulmonary arteries were enlarged and showed increased pulsation. Although in such cases, undue prominence rather than concavity of the pulmonary conus may be expected, the middle segment of the left cardiac border appeared concave in the postero-anterior teleradiogram in one patient in the present series, Case 4, where there was associated transposition of the great vessels without evidence of pulmonary stenosis. With the exception of Case 9, a concave left middle segment was noted in all patients in the present series, irrespective of cardiac shape.

Descriptions of the right cardiac border in tricuspid atresia have varied. Brown (1950), speaks of exaggerated convexity, Gasul *et al.* (1950) mention diminished projection of the right cardiac border, and Wittenborg *et al.* (1951) quote diminished convexity or actual concavity as characteristic of tricuspid atresia. Astley *et al.* (1953) observed only slight extension of the right cardiac border to the right of the spine in 11 of their 16 patients. In the present series of 9 patients the right heart border was less prominent than normal in 6 and was conspicuously flattened in 4 of these 6 (Table II). In view of the dilatation of the right atrium that occurs in tricuspid atresia this is unexpected. Wittenborg *et al.* (1951) believe that the diminished prominence of the right cardiac border is due directly to hypoplasia of the right ventricle, while Schnitker (1952) suggests that a large right atrium may not appear so because of the diminution in size of the right ventricle. Astley *et al.* (1953) observed a similar right cardiac border in 13 of 41 patients with the tetralogy of Fallot, and therefore considered that this feature was not of great diagnostic importance in tricuspid atresia. However, only 3 of a series of 20 patients with the tetralogy of Fallot studied in this unit showed diminished prominence of the right cardiac border and since this appearance was not observed in any of 8 cases of transposition of the great vessels, the frequency of this sign in tricuspid atresia suggests that it may be of diagnostic value, and being dependent upon a hypoplastic right ventricle is more likely to be found than some other radiological features that reflect anatomical abnormalities not always present.

According to Taussig (1947), the small size of the pulmonary artery is solely responsible for the narrow vascular pedicle, seen in both anteroposterior and left anterior oblique views, in tricuspid atresia. She believes that the narrow vascular pedicle associated with tricuspid atresia can be distinguished from that of the tetralogy of Fallot and of transposition of the great vessels. In Fallot's tetralogy the narrow pedicle is due to a combination of pulmonary artery hypoplasia and rotation of the great vessels, and in transposition of the great vessels to rotation alone; therefore, in both conditions the pedicle is normal or only slightly narrowed in the left anterior oblique view. Wittenborg *et al.* (1951) mentioned a narrow vascular pedicle as a sign characteristic of tricuspid atresia, but did not record its incidence in their series. Astley *et al.* (1953) found it in 8 of their 16 patients and in the present series 5 of the 8 cases examined radiologically had a narrow vascular pedicle in the frontal projection.

In the left anterior oblique position, prominence of the posterior border combined with diminished forward projection of the heart are signs usually regarded as evidence of a large left ventricle and a small right ventricle respectively, and were considered characteristic of tricuspid atresia by Taussig (1947) and Brown (1950). Astley *et al.* (1953) thought that a prominent upper part of the posterior border in this position, due to left atrial enlargement, was a more reliable feature of tricuspid atresia and stated that left atrial enlargement in a cyanosed patient should suggest tricuspid atresia.

Diminished projection of the anterior border was not accepted as evidence of a hypoplastic right ventricle by these authors who noted this appearance in the tetralogy of Fallot. Abrams and Alway (1951) also regarded this as a misleading sign and commented that, in congenital cardiac anomalies with right ventricular

hypertrophy, the right ventricular shadow sometimes failed to project anterior to the aorta in the left anterior oblique position owing to the anterior position of the aorta. They also described a case of tricuspid atresia, with a hypoplastic right ventricle, where there was an abnormally prominent anterior projection in the left anterior oblique view due to a large right atrium. There was abnormal prominence of the posterior border in the left anterior oblique position in 5 patients in this series and in 4 of these (Fig. 4, Table II) the prominence involved the upper part of the posterior border. In 3 patients there was no abnormal prominence of the posterior border and in Case 5, where autopsy showed a very large left ventricle and a small left atrium, there was a wide margin between the heart shadow and the vertebral column. There was a straight anterior cardiac border in the left anterior oblique position in 2 patients in this series one of whom had transposition of the great vessels. The anterior cardiac outline was of the normal convex appearance and was not unduly displaced backward from the sternum in 5 cases (Table II). Examination of the heart in the left anterior oblique position may not help in diagnosis since, despite the considerable anatomical differences there may be identical appearances in patients with tricuspid atresia, Fallot's tetralogy, and transposition of the great vessels. Since a wide range of anomalies are associated with triscuspid atresia, there is no constant radiological appearance of the heart, but when present, a " square " heart and diminished projection of the right cardiac border in the frontal projection are useful diagnostic pointers.

The vascularity of the lungs has been commented on by many authors and Astley *et al.* (1953) considered that cases of tricuspid atresia could be divided into two distinct groups, those with normal or increased pulmonary vascularity and those with reduced pulmonary vascularity. Wittenborg *et al.* (1951) thought that increased vascularity, with or without hilar dance almost invariably indicated associated transposition of the great vessels. Kroop (1951) supported this interpretation of increased pulmonary vascularity but noted that the lung markings were not necessarily prominent when there was transposition without pulmonary stenosis, and that they might be normal when there was pulmonary stenosis, with or without transposition of the vessels. Astley *et al.* (1953) did not necessarily associate well-vascularized lungs with the presence of transposition of the great vessels as some of their patients with this complication had oligæmic lung fields. Their opinion is supported by the present series where only Case 4 of the three with increased pulmonary vascularity had transposition of the vessels. Case 1, the oldest in the present series, showed increased vascularity of the lungs from a dense collateral circulation.

Increased pulmonary vascularity contraindicates surgical treatment at any age. In infants it seems reasonable to assume, as Astley *et al.* (1953) have done, that pulmonary oligæmia is the most important criterion for surgical treatment but it should be borne in mind that the pulmonary artery may be too small to allow it to be anastomosed to another vessel.

Angiocardiography

Angiocardiographic appearances that have been considered of diagnostic importance in tricuspid atresia are early filling of the left atrium through an atrial septal defect (Brown, 1950; Campbell and Hills, 1950; Denolin *et al.*, 1950; Cooley *et al.*, 1950; Soulié, 1952; Astley *et al.*, 1953; Marder *et al.*, 1953; Goodwin *et al.*, 1953; and Fig. 5 and 6), a clear triangular area between right atrium and left ventricle (Campbell and Hills, 1950; Soulié, 1952; Marder *et al.*, 1953; Astley *et al.*, 1953; and Fig. 5) and opacification of a rudimentary right ventricle in the triangular clear area (Campbell and Hills, 1950; Astley *et al.*, 1953; Goodwin *et al.*, 1953; and Fig. 5).

Assessment of the early filling of the left atrium is more reliable using lateral angiocardiograms but filling can usually be recognized in the postero-anterior view particularly when there is opacification of the left auricular appendage (Fig. 5 and 6). The clear triangular area in the P-A angiocardiograms is due to absence of the right ventricular inflow tract. This sign, called " the right ventricular window " by Campbell and Hills (1950), was observed in all our 8 patients who had this investigation (Fig. 5). Early filling of the left atrium and a " right ventricular window " are angiocardiographic signs that must be present to support a diagnosis of tricuspid atresia, since patients with this anomaly will show early filling of the left atrium unless there is an associated persistent foramen primum which allows contrast medium to flow directly from the right atrium to the left ventricle as in Case 5 (Fig. 6).

Opacification of the rudimentary right ventricle in the right ventricular window provides confirmatory evidence of tricuspid atresia but this occurs only if there is a ventricular septal defect.

Absence of this sign suggests there is not such a defect but does not contraindicate a diagnosis of tricuspid atresia. The patients in the present series, where this sign had been observed, who were examined at autopsy (Cases 2, 3, and 5) all had a ventricular septal defect (Fig. 12).

After it leaves the left ventricle the course of the contrast medium provides information of associated anatomical lesions and of the pulmonary vascularity. The origins of the great vessels are most clearly seen on the lateral angiocardiograms which allow associated transposition to be recognized (Fig. 5 and 6).

Cardiac Catheterization

Cardiac catheterization has rarely been carried out in the reported patients with tricuspid atresia. In Cases 3 and 9 in the present series where this investigation was performed, it was impossible to introduce the catheter into a right ventricle and the tip passed repeatedly through an atrial septal defect into the pulmonary veins and left ventricle (Fig. 7 and 8). Geraci *et al.* (1948) and Holling and Zak (1950) reported similar findings. Estimations of oxygen saturation of blood samples taken at cardiac catheterization showed that the pulmonary venous blood was normally saturated with oxygen and that there was mixing of the systemic and pulmonary venous bloods in the atria. Failure to enter the right ventricular cavity provides confirmatory evidence of tricuspid atresia although occasionally in other patients with large atrial septal defects it is difficult to direct the tip of the catheter through the tricuspid valve. There is usually no indication for cardiac catheterization where angiocardiography is available since this more often provides diagnostic evidence of tricuspid atresia.

Discussion of Pathology

Edwards and Burchell (1949) elaborated the classification of tricuspid atresia made by Kühne (1906) and defined the characteristic defects common to all varieties of the disease as atresia of the tricuspid orifice, patency of the atrial septum, usually a patent foramen ovale, and a large mitral orifice leading into a large left ventricle. In the present series Cases 2, 3, and 8 illustrate the features of Type 1b tricuspid atresia defined by these authors. In Case 5 small deformed leaflets of the tricuspid valve were probe-patent and in addition there was a patent foramen primum which produced a common A-V canal. This latter abnormality is a common cardiac malformation in Mongolian idiocy which was present in Case 5.

(*A*) *The classical features of uncomplicated tricuspid atresia.* (Cases 2, 3, and 8; Fig. 9 and 10). All varieties of tricuspid atresia function as two-chambered hearts, one chamber consisting of the atria in communication with each other through a patent foramen ovale and the other consisting of the left ventricle. Venous blood from pulmonary and systemic circulation flows into the left atrium and thence through the mitral valve into the left ventricle and aorta. The abnormally high blood flow is associated with dilatation and hypertrophy of the left atrium, widening of the mitral ring, and hypertrophy of the left ventricle. There is usually no tricuspid orifice although in some cases bands of fibrous tissue replace the tricuspid valve which may be probe-patent (Case 5). Such cases of tricuspid stenosis are indistinguishable in life from tricuspid atresia.

Edwards and Burchell (1949) recognized four types of tricuspid atresia. In the first (Type 1a) there is pulmonary atresia as well as tricuspid atresia but no transposition of the great vessels or ventricular septal defect. The right ventricle is tiny and its cavity forms merely a slit in the hypertrophied wall of the left ventricle. Some cases of apparent single ventricle may be examples of tricuspid atresia in which the right ventricle is microscopic. The pulmonary artery is hypoplastic and the blood supply to the lungs is via a patent ductus arteriosus.

The second (Type 1b) is the commonest form of tricuspid atresia. Blood to the lungs is carried from a small but functioning right ventricle through a stenosed pulmonary valve to a hypoplastic but patent pulmonary artery. A ventricular septal defect allows the passage of blood from left to right ventricle. This was considered to be the anatomical arrangement in all except Case 4 in the present series (Fig. 9 and 10).

Transposition of the great vessels associated with stenosis of the right ventricular outflow tract occurs in the third type (Type 2a). There may be a pulmonary valvular or infundibular stenosis.

The fourth (Type 2b) is anatomically identical with the third form apart from the absence of pulmonary stenosis.

In the first three types of tricuspid atresia there is an anatomical barrier to the flow of blood to the lungs. In Type 1a the barrier of pulmonary atresia is absolute and blood must pass to the lungs through a patent ductus arteriosus or bronchial arteries. A ventricular septal defect and a hypoplastic pulmonary artery provide the resistance in Type 1b while in Type 2a where the pulmonary artery arises from the left ventricle there is pulmonary or infundibular stenosis. These anatomical barriers lead to pulmonary hypotension and blood of high viscosity flows through the pulmonary vessels at low tension as in Fallot's tetralogy.

The fourth type of tricuspid atresia (Type 2b) is functionally quite distinct from the other three for blood flows at high pressure from the left ventricle to the lungs. The pulmonary arteries are subjected to pulmonary hypertension as in Eisenmenger's complex.

The striking histological changes described in Case 2 (who had Type 1b tricuspid atresia (Fig. 13)), are probably related to the abnormal pulmonary circulation since anoxæmia, polycythæmia, and a slow blood flow are ideal conditions for the development of thrombi.

Similar histological appearances have been found in the lungs of patients with Fallot's tetralogy (Rich, 1948; Hales and Liebow, 1948) and would be expected in the lungs of patients with tricuspid atresia where there is also a sluggish blood flow; but not in Type 2b where it is probable that the small pulmonary vessels would show features associated with pulmonary hypertension similar to those described in Eisenmenger's complex (Brown *et al.*, 1955), patent ductus arteriosus with pulmonary hypertension (Whitaker *et al.*, 1955), and ventricular septal defect with pulmonary hypertension (Heath *et al.*, 1956).

(*B*) *Features of tricuspid atresia complicated by persistent foramen primum.* (Case 5; Fig. 11 and 12). Case 5 with congenital tricuspid stenosis had at autopsy features characteristic of tricuspid atresia, viz: tricuspid atresia, patent foramen ovale, a big left ventricle and a small right ventricle and in addition, a persistent foramen primum producing in this patient a common atrioventricular canal (Fig. 11). This additional lesion, which is common in mongols (Edwards *et al.*, 1954) accounted for the angiocardiographic findings. The absence of left atrial filling was due to the contrast medium passing from the large right atrium into the left ventricle. The central cyanosis in Case 5 followed admixture of systemic and pulmonary venous blood in the left ventricle and not in the atria as in uncomplicated tricuspid atresia.

Pathogenesis

Various theories have been advanced to explain tricuspid atresia. An account has already been given by one of us (Brown, 1950) of the theory suggesting that the lesion results from unequal division of the common A-V orifice by fusion and adhesion of the anterior and posterior cushions to the right wall. Chronologically such an event occurs at about the fourth week of intrauterine life. At this stage the anterior and posterior cushions of the atrial canal have fused except at their right and left extremities. These extremities are destined to become the right and left A-V ostia, and by thickening of the endocardium right and left endocardial cushions are formed from which develop the tricuspid and mitral valves. The developing interatrial septum joins with the middle part of the fused anterior and posterior cushions, and the developing inter-ventricular septum joins the right endocardial tubercule causing some narrowing of the right ostium. This is only temporary, for later the ventricular septum is rotated so that its anterior part comes to the right and its posterior part to the left. This rotation brings it into alignment with the atrial septum. It seems likely that in tricuspid atresia normal rotation of the ventricular septum fails, and the right ostium is compressed and finally obliterated. The associated ventricular septal defect is a true defect and represents failure of union between the bulbar septum and the ventricular septum owing to lack of rotation. Such a membranous ventricular septal defect was found in Case 8. Similarly the

frequent coincidence of pulmonary atresia or pulmonary conus stenosis suggests failure of torsion and unequal division of the bulbus and truncus. Tricuspid atresia has sometimes been ascribed to the effects of fœtal endocarditis, and occasionally a case may be seen in which there are rudimentary and fused valve leaflets as in Case 5. Much more often the site of a tricuspid valve is a smooth fibrous membrane, or trabecular muscular tissue in which no suggestion of valvular structure can be found. The occurrence of dextroposition or of complete transposition in many cases lends strength to a developmental origin.

Assuming the atresia to arise at about the fourth week, such abnormalities as the accompanying patent foramen ovale, persistent ostium secundum, patent ductus arteriosus, or hypoplasia of the pulmonary tract are really secondary abnormalities determined by the need of a circulation to the lungs on the one hand, and by altered dynamic changes in the blood flow on the other. The extent of these secondary defects determines whether the heart will function as a biloculate or triloculate heart.

Edwards (1953) believes that there is evidence against the view that tricuspid atresia is caused by an eccentric ventricular septum, for in cases of isolated pulmonary atresia, although the left ventricle is large, the right ventricle small, and the ventricular septum eccentric, tricuspid atresia need not be associated. Furthermore if tricuspid atresia were due to an eccentric ventricular septum, a membranous ventricular septal defect would always be expected due to failure of fusion of the ventricular and bulbar septa but in the present series 3 of the 4 cases (Cases 2, 3, and 5) had muscular defects.

Differential Diagnosis

Tricuspid atresia is most likely to be confused with Fallot's tetralogy but it must also be differentiated from the other forms of congenital heart disease that present with cyanosis without the signs of pulmonary hypertension. These include pulmonary stenosis with reversal of shunt through a septal defect, Ebstein's disease, some forms of transposition of the great vessels, some forms of persistent truncus arteriosus, and other more primitive types of congenital heart disease such as single ventricle, common atrio-ventricular canal, and biloculate and triloculate hearts. It is not possible to differentiate between tricuspid atresia and the more severe forms of congenital tricuspid stenosis associated with an atrial septal defect.

It seems probable that on clinical examination the majority of cases of tricuspid atresia will be diagnosed as suffering from Fallot's tetralogy. Occasionally, as in Cases 1 and 4 of the present series a left ventricular thrust at the apex may indicate the correct diagnosis. In our experience this is the only clinical sign that suggested a diagnosis of tricuspid atresia. Although Taussig (1947) and Astley *et al.* (1953) considered presystolic hepatic pulsation in infants and abnormal presystolic pulsation in the neck veins of diagnostic importance, the jugular venous pulse was of no value in differential diagnosis in the present series.

Five of the present patients had abnormally prominent presystolic waves in the jugular venous pulse (Table I, Fig. 14) but clinically these were in no way different from the abnormal pulsations seen in patients with pulmonary stenosis and reversal of shunt through a septal defect, or with forms of congenital heart disease associated with pulmonary hypertension.

Differentiation of tricuspid atresia from Fallot's tetralogy and other forms of cyanotic congenital heart disease not associated with pulmonary hypertension will generally depend on electrocardiographic and special investigations. Left axis deviation in the cardiogram which is almost invariable in tricuspid atresia will generally make this distinction. Rarely such conditions as persistent truncus, Ebstein's disease, and transposition of the great vessels may be associated with left axis deviation in the electrocardiogram and such anomalies can be distinguished from tricuspid atresia by angiocardiography. Early filling of the left atrium and a " right ventricular window " on angiocardiography are diagnostic of tricuspid atresia in the presence of left axis deviation in the cardiogram. In conditions associated with pulmonary stenosis and pulmonary hypertension where

there is a reversal of shunt through an atrial septal defect the cardiogram shows right axis deviation and right ventricular hypertrophy. Patients with Ebstein's disease may have left axis deviation in the cardiogram and show early filling of the left atrium in the angiocardiograms but this anomaly will always be recognized by other characteristic clinical, cardiographic, and radiological features and by the enormous size of the right atrium in angiocardiograms (Brown *et al.*, 1955*a*). Tricuspid atresia can easily be distinguished clinically from congenital anomalies associated with severe pulmonary hypertension such as Eisenmenger's complex, patent ductus arteriosus, ventricular and atrial septal defect associated with reversal of flow, and idiopathic pulmonary hypertension, by the absence of the classical clinical, cardiographic, and radiological signs of pulmonary hypertension which dominate this group of cases.

Prognosis and Treatment

The prognosis in tricuspid atresia is poor; Campbell and Deuchar (1953) pointed out that the mortality was higher in tricuspid atresia than in any other type of congenital heart disease except pulmonary atresia and transposition of the aorta and pulmonary trunk.

Astley *et al.* (1953) noted that many patients with tricuspid atresia die in the first few months of life. This high mortality in infancy is presumably due to the effect of closure of a patent ductus on the pulmonary blood flow and, as pointed out by Kroop (1951), is especially liable to occur in those children without transposition but with pulmonary stenosis. Edwards (1953) believes that cases of tricuspid atresia with a non-functioning right ventricle or with transposition of the great vessels and no pulmonary stenosis rarely survive infancy and that patients with no transposition of the great vessels, a ventricular septal defect and a small right ventricle have a slightly better prognosis. He also considers that patients with transposition of the great vessels and pulmonary stenosis may reach adult life, as did the often misquoted woman patient of Hedinger (1915) who lived to the age of 56. This opinion is not in complete agreement with that expressed by Astley *et al.* (1953) who thought that death was likely to occur in infancy in patients with oligæmic lungs and that the prognosis was much more favourable when a pulmonary artery of normal calibre was transposed to the left ventricle. Since the cases reported by Hedinger (1915) and Geraci *et al.* (1948), who survived to adult life, all had transposition of the great vessels and pulmonary stenosis, associated transposition appears to be of favourable prognostic importance when combined with pulmonary stenosis. Paradoxically, the oldest patient in the present series (Case 1), who is still alive at the age of 45 years, has hypoplasia of the pulmonary arteries and no transposition. However, the radiological and angiocardiographic findings in this patient suggested that she had a well-developed bronchial collateral circulation which presumably accounts for her survival. It is impossible from the present series to make any dogmatic statements on the influence of associated anomalies on survival, since three of the patients died after having an operation.

The high mortality in infants with tricuspid atresia and pulmonary stenosis without transposition has encouraged operative treatment. Campbell and Deuchar (1953) reported the results of surgical treatment in 7 cases of tricuspid atresia with a non-functioning right ventricle: 2 died within a year and the other 5 did well, 3 of these 5 remaining well three years after operation, including a patient aged 19. They considered that the results of operation in tricuspid atresia were in general not as good as Fallot's tetralogy but in 3 of their cases the improvement was just as great. They thought that the heart size was the best guide to whether a patient with tricuspid atresia was likely to maintain improvement after operation and that if the cardio-thoracic ratio was under 54 per cent a good result might last for several years, but if it was more than 60 per cent prognosis was less certain. They quoted a mortality of 26 per cent within six months of operation in a series reported by Taussig *et al.* (1951). Gasul *et al.* (1949) have apparently obtained successful anastomoses using Pott's operation in children with tricuspid atresia. Astley *et al.* (1953) suggested that operative treatment should be extended to all patients with tricuspid atresia and pulmonary

stenosis, and thought that the demonstration of pulmonary oligæmia was the sole criterion necessary before advising thoracotomy if they were satisfied that the atrial septal defect was large enough to allow a good flow of blood from right to left. Our experience of surgical treatment in patients who would have been considered most suitable on the criteria suggested by these authors has been disastrous. All three patients (Cases 2, 3, and 5) succumbed rapidly soon after operation. Histological examination of the lungs in Case 2 showed extensive intravascular thromboses in the muscular pulmonary arteries and veins suggesting that the pulmonary vascular bed had not been able to accept the increased blood supply directed to it through the shunt (Fig. 13). We believe that if operation is to be effective it must be carried out before the changes in the small pulmonary vessels have had time to develop and is more likely to be successful when performed in infants. The pulmonary vascular bed in Case 8 who died from congestive cardiac failure at the age of three months was normal.

Summary

Eight patients with congenital tricuspid atresia and one with congenital tricuspid stenosis are described, with an account of the autopsy findings in four of them.

Characteristic symptoms were breathlessness on exertion, cyanosis, and recurrent chest infections but these are not specific to tricuspid atresia. On physical examination, central cyanosis and finger clubbing occurred in all, and a præcordial systolic murmur in all but one. A palpable thrust at the apex indicated left ventricular hypertrophy in two patients but in the others the clinical signs were suggestive of Fallot's tetralogy. The jugular venous pulse, although abnormal in six, was not characteristic enough to be diagnostic.

The electrocardiogram was recorded in 8 patients and showed left axis deviation in all. This was considered a most important diagnostic feature since it excluded the diagnosis of Fallot's tetralogy and suggested the probability of tricuspid atresia. Abnormally tall P waves occurred in only two patients.

Radiological examination was suggestive of tricuspid atresia in only two of the patients who showed square-shaped hearts. Generally, in tricuspid atresia the cardiac silhouette will be compatible with a diagnosis of Fallot's tetralogy.

Angiocardiography provided confirmatory diagnostic evidence in 7 of the 8 patients in whom it was done. Early filling of the left ventricle and a " right ventricular window," sometimes showing a diminutive right ventricle later, are pathognomonic signs in the antero-posterior views. The origin of the great vessels was well seen in the lateral views and there was evidence of transposition in only one of the patients.

Cardiac catheterization was performed in two patients. It provided anatomical confirmation of an atrial septal defect and suggested tricuspid atresia from inability to introduce the catheter into the right ventricle. Generally it is an unnecessary diagnostic procedure.

Autopsy examination of the heart in three cases showed classical abnormalities of tricuspid atresia and in a fourth, who was a mongol, an associated patent foramen primum.

Histological examination of the small pulmonary vessels was normal in the youngest patient aged 3 months, but in another aged 7 years showed great reduction of the pulmonary vascular bed due to extensive thrombosis in pulmonary arteries and veins. These pathological changes offered an explanation of the failure of anastomotic operations in four of our patients. It is suggested that anastomotic operations are more likely to be successful when carried out in infancy before the secondary pulmonary vascular changes develop.

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CONGENITAL HEART DEFECTS FOLLOWING MATERNAL RUBELLA DURING PREGNANCY

BY

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The occurrence of various congenital anomalies, including heart defects, in children whose mothers had suffered from rubella during pregnancy was originally described by Gregg (1941) in Australia and these observations have been confirmed by many other workers. There is, however, surprisingly little detailed information available about the particular types of congenital heart defect that may occur. The matter is of considerable interest to cardiologists, for maternal rubella is one of the few known ætiological factors in congenital heart disease.

In Gregg's (1941) original report a patent ductus arteriosus was found at post-mortem examination in 3 infants. Swan *et al.* (1943) also found a patent ductus arteriosus at necropsy in 3 patients, and in one of these a small ventricular septal defect was present as well. Dogramaci and Green (1947) in a series of 434 cases of congenital heart disease found 5 patients whose mothers had suffered from rubella during pregnancy; patent ductus arteriosus occurred twice, Fallot's tetralogy once, and ventricular septal defect twice, one of these with pulmonary stenosis as an additional lesion. Jackson (1950) found seven children whose mothers had suffered from rubella during pregnancy among 343 cases of congenital heart disease proven at operation or at post-mortem examination: all seven had a patent ductus arteriosus and one of these had pulmonary stenosis and a small ventricular septal defect as well. Campbell (1949) among 243 cases found 4 following maternal rubella, all with Fallot's tetralogy and one with an atrial septal defect as well and two with cataract as well: two of these four followed rubella in 1940 during the same epidemic that was so severe in Australia. Gibson and Lewis (1952) reported 17 cases following maternal rubella, one each of atrial septal defect, ventricular septal defect, and Fallot's tetralogy, and in the remaining 14 a patent ductus arteriosus, combined with ventricular septal defect in two cases and with pulmonary stenosis and coarctation of the aorta in one each.

Material

This report is based on experience at the Royal Alexandra Hospital for Children over the five years up to December, 1953. A total of 426 patients suffering from congenital heart disease was examined during this period, and there were 44 who presented with a history of maternal rubella during pregnancy. Twenty-one of these were referred to the Congenital Heart Disease Clinic as part of a special survey of the rubella problem; the remainder were referred for opinion by other physicians. The ages of these patients ranged from 3 months to 12 years. A full blood count, a standard 12-lead electrocardiogram, and radiological examination were carried out in all cases. Of the 27 patients considered to have an actual cardiac defect, the diagnosis was confirmed in 7 at operation, in 6 by angiocardiography or cardiac catheterization, and in 7 at post-mortem examination.

Results

Some details of the 44 patients are presented in Table I. Seventeen of them were considered

CONGENITAL HEART DISEASE FOLLOWING MATERNAL RUBELLA

Diagnosis	No. of cases	Associated cardiac defects	Operation	Post-mortem	Angio. or catheter	Other anomalies			Rubella during pregnancy (months)					
						Deaf	Cataract	Both	1	2	3	4	5	7
Innocent systolic murmur	17	—	—	—	1	12	—	5	5	5	7			
Patent ductus arteriosus	13	Small VSD—2 Mild PVS—2	6	6	1	4	5	—	1	4	1		1	1
Ventricular septal defect	4	—	—	—	—	1	1	1	3	1				
Atrial septal defect	3	—	—	—	2	1	—	2	1	2				
Pulmonary stenosis	1	—	—	—	—			1	1					
Aortic stenosis	1	—	—	—	—	1					1			
Coarctation of the aorta	1	Aortic stenosis	—	—	—	—	—			1				
Tetralogy of Fallot	2	—	—	—	2	—	—	—	1		1			
Eisenmenger Complex	1	—	—	—	1	—	—	—						
Transposition of great vessels	1	—	1	1	—	—	—				1			

to have a normal heart with an innocent systolic murmur. The criteria adopted in making this diagnosis have been discussed elsewhere (Stuckey, 1955), and may be stated briefly as a mid-systolic murmur of slight or moderate intensity, of short duration occupying no more than half of systole, usually loudest in the left parasternal line, and with no other abnormality to be found on clinical, radiological, or electrocardiographic examination.

In the 27 patients considered to have a congenital cardiac defect a wide variety of lesions was found. Thirteen had a patent ductus arteriosus, 4 a ventricular septal defect, 3 an atrial septal defect, 2 the tetralogy of Fallot, and one each suffered from aortic stenosis, pulmonary stenosis, coarctation of the aorta, the Eisenmenger complex, and transposition of the great vessels. Apart from patent ductus arteriosus, the relative incidence of the various lesions agreed closely with that found in the general population (Stuckey, 1954). Female preponderance (11:2) was found in those with a patent ductus arteriosus, and male preponderance (12:5) in those with an innocent systolic murmur, agreeing with the sex tendencies usually found in these conditions (Shapiro, 1939; Brown, 1950; and Stuckey, 1955, *a* and *b*).

INCIDENCE OF CONGENITAL HEART LESIONS FOLLOWING MATERNAL RUBELLA

An attempt has been made to estimate the incidence of congenital heart defects following maternal rubella in the year 1940, at the height of the rubella epidemic in Australia. Various figures have been given for the proportion of live births showing any type of congenital anomaly following maternal rubella during pregnancy. Some Australian figures are 90 per cent (Swan *et al.*, 1943), 30 per cent (Patrick, 1948), 75 per cent (Dods, 1951), and 70–80 per cent (Collins, 1953). Figures from America based on prospective studies are much lower (Ober *et al.*, 1947; Ingalls and Purshottam, 1953). After discussion with others who saw the 1940 epidemic here, 50 per cent has been taken as a reasonably conservative figure for that particular time and place. It might be expected that, like any other virus, the virulence of rubella for the host tissues, fœtal or otherwise, would vary from time to time and from place to place.

The number of live births with congenital defects of any type following maternal rubella in New South Wales in the year 1940 was 178 (Gregg *et al.*, 1945) and if we assume a 50 per cent incidence of congenital anomalies, then the total number of live births following maternal rubella in that year would have been about 356.

Of our 27 patients with congenital heart defects following maternal rubella, 10 with patent ductus arteriosus and 6 with other congenital heart defects were born in 1940. The incidence therefore was 28 per thousand for patent ductus arteriosus, and 17 per thousand for other

congenital heart lesions. For comparison, the normal incidence of congenital heart disease in the general population aged 3 months to 15 years has been given as 1·8 per thousand (Macmahon *et al.*, 1953), and patent ductus arteriosus constitutes 18 per cent of these (Macmahon *et al.*, 1953; Stuckey, 1954). The normal incidence of patent ductus arteriosus may thus be given as 0·3 per thousand, and that of the other congenital heart defects as 1·5 per thousand.

On these figures the incidence of patent ductus arteriosus in children born of mothers who had suffered from rubella during pregnancy in New South Wales in 1940 was about 88 times the normal, and the incidence of other congenital heart lesions about 11 times the normal.

Multiple Cardiac Defects following Maternal Rubella

In our own series the combination of a patent ductus arteriosus with another congenital heart lesion was found at post-mortem examination in 4 patients, a small ventricular septal defect in 2 cases, and pulmonary valve stenosis in 2 cases. Our patient with caorctation of the aorta was considered to have aortic stenosis as well on clinical grounds. Other observers have reported the association of patent ductus arteriosus with ventricular septal defect (Swan *et al.*, 1943; Jackson, 1950; Gibson and Lewis, 1952), with pulmonary valve stenosis (Jackson, 1950; Gibson and Lewis, 1952), with coarctation of the aorta (Gibson and Lewis, 1952), and with aortic valve lesions (Bonham-Carter *et al.*, 1955). On the published figures, an additional cardiac lesion is likely to be present in about one-quarter to one-third of these patients with a patent ductus arteriosus.

Cardiac Defects and Other Anomalies probably Due to Maternal Rubella

In this series the association of a cardiac defect with deafness or cataract or both occurred in 9 of 13 patients with a patent ductus arteriosus, in 3 of 4 with a ventricular septal defect, in 3 with an atrial septal defect and in one each with pulmonary stenosis and aortic stenosis. Other observers (Dogramaci and Green, 1947) have reported the association of Fallot's tetralogy and cataracts in one patient.

Discussion

It has been generally accepted that maternal rubella during pregnancy is causally related to a patent ductus arteriosus in the child, and the present report supports this view. In regard to the other congenital heart lesions, we must consider the increased incidence, the association with patent ductus arteriosus in the case of ventricular septal defect, pulmonary stenosis, aortic valve lesions and coarctation of the aorta, and the association with other specific evidence of fœtal damage (deafness, cataracts). All these things suggest that maternal rubella may produce a wide variety of congenital heart defects in the child.

It has been shown that patent ductus arteriosus occurred about eight times more frequently than the other congenital heart lesions, compared with the normal relative incidence in the general population. A possible explanation can be offered for this interesting finding. The cardiac septa, the main vessels, and their valves are only susceptible to damage by environmental factors for a short period of some 4 or 5 weeks of fœtal life while they are being actively formed, the so-called "critical period" for these structures (Dods, 1951). The ductus arteriosus, on the other hand, is present for many months of fœtal life and for a short time after birth, and whatever the mechanism of final closure it is conceivable that it could be damaged at any stage. The greater incidence of patent ductus arteriosus in these children may thus merely reflect the longer time that this structure is at risk. If this explanation is accepted, the fact that patent ductus arteriosus does not predominate unduly over other congenital cardiac defects in the general population may suggest that genetic rather than environmental factors are responsible for the great bulk of cases of congenital heart disease.

Another point of interest is that whatever is responsible for the strong female preponderance in patent ductus arteriosus still operates in the post-rubella cases. Eleven of our 13 patients with a patent ductus arteriosus were girls.

Most of our post-rubella cases resulted from the rubella epidemic of 1940 and succeeding years, but they continue to account for about 2 per cent of all congenital heart defects seen at this hospital. Since the present series closed we have observed four additional cases, one of aortic stenosis and three of patent ductus arteriosus, one of these with pulmonary stenosis as an additional lesion. The incidence in any community will obviously depend on the incidence and virulence of rubella affecting women during pregnancy.

Close inquiry amongst patients attending the Congenital Heart Disease Clinic over the last seven years regarding other illnesses complicating pregnancy has failed to incriminate any other infectious fever as a cause of congenital heart disease. In only three instances was such an illness reported, mumps twice and varicella once, and this small incidence may well have been due to chance. This does not deny the possibility that other infectious diseases in the mother may damage the developing fœtus, and may only reflect the peculiar epidemiological characteristics of rubella and the greater susceptibility of adults, including pregnant women, to this disease.

Summary

A wide variety of congenital heart defects in the child may follow maternal rubella during pregnancy. Twenty-seven such patients are reported, of whom 13 had a patent ductus arteriosus, 4 a ventricular septal defect, 3 an atrial septal defect, 2 the tetralogy of Fallot and one each aortic stenosis, pulmonary stenosis, coarctation of the aorta, the Eisenmenger complex and transposition of the great vessels.

Patent ductus arteriosus occurred about eight times more frequently than other forms of congenital heart disease compared with the normal relative incidence in the general population. A possible reason for this is suggested.

Thanks are due to Professor Lorimer Dods, of the Institute of Child Health, for his interest and encouragement.

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THE EFFECTS OF RESERPINE ON HYPERTENSIVE PATIENTS OVER A PERIOD OF TWO YEARS

BY

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To justify the use of a drug in the routine treatment of hypertension it should be capable of reducing the diastolic and systolic blood pressures by 20 mm. Hg or more throughout the day and tolerance to its action should not develop on prolonged administration; the therapeutic dose should be considerably less than the toxic dose and since indefinite administration is required, the side-effects should not interfere with either the patient's capacity for work or his enjoyment of life. It was the purpose of this study to determine how far these requirements are fulfilled by reserpine, a pure crystalline alkaloid obtained from *Rauwolfia serpentina.*

Reserpine was isolated by Muller *et al.* (1952) from *Rauwolfia serpentina* and pharmacological studies have been published by a number of investigators. Bein *et al.* (1953) stated that its activity on experimental animals is characterized by sedation and hypnosis, a lowering of the blood pressure, a reduction in respiratory volume, bradycardia, miosis, increased intestinal activity, and a lowering of body temperature. The sedative action chiefly affects the motor cortex and inhibits the stimulant action of caffeine. The mode and site of action of reserpine is not known but animal and clinical studies suggest that its action is on the central nervous system (Winsor, 1954). Plummer *et al.* (1954) consider that the most likely area at which the drug could bring about the observed alteration in autonomic balance is in the hypothalamic region.

Trappold *et al.* (1954) examined the cardiovascular and respiratory effects of reserpine in the dog; their evidence suggests that the hypotensive action is due to an inhibition of nerve impulses through or from a higher brain centre, such as the hypothalamus. Chen *et al.* (1954) showed that reserpine may cause an increase in excitability or conductivity of parts of the central nervous system. From a later paper (Chen *et al.*, 1954) it appears that the antagonism between reserpine and epanutin is competitive in nature, a facilitatory and an inhibitory effect respectively acting on the spread of the seizure discharge.

Materials and Methods

Thirty-five hypertensive patients were chosen for this study. One was excluded from the analysis of results, as treatment had to be discontinued after 12 weeks' reserpine therapy owing to the development of a state of extreme depression. The criteria for inclusion were capability of treatment on an out-patient basis, an average blood pressure of greater than 150/100 mm. mercury and/or a mean blood pressure (diastolic + 1/3 pulse pressure) of 115 mm. mercury. Otherwise there was no selection. Patients were asked to report to the clinic as frequently as possible. For most patients this was every two weeks, although there was a variation from one to four weeks.

The trial of reserpine was planned so that inert tablets were administered to patients for from six to nine months (observation period), reserpine tablets in a dose of one to two milligrams daily were then administered for 12 months (therapeutic period) and finally, patients were divided into two groups, one of which

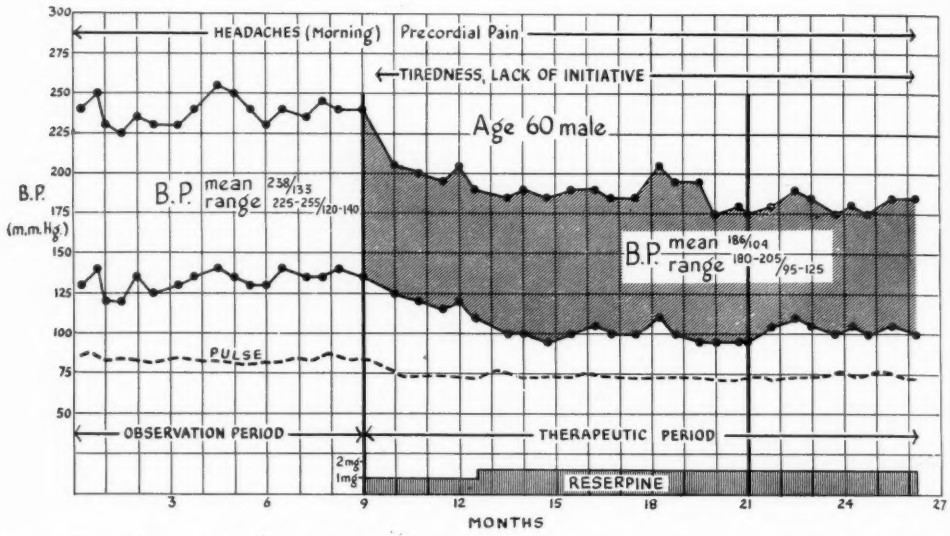

FIG. 1.—The variations in the blood pressure, pulse rate, and symptomatology of a patient over a period of 26 months. Reserpine was administered from the ninth to twenty-sixth month.

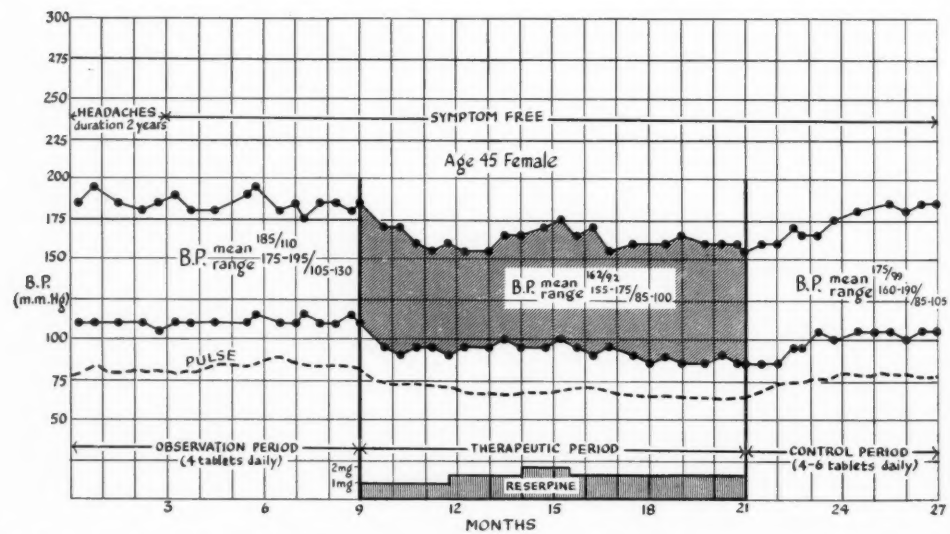

FIG. 2.—The variations in the blood pressure, pulse rate, and symptomatology of a patient over a period of 27 months. Reserpine was administered from the ninth to twenty-first month.

received reserpine and the other inactive tablets for a further 3 to 6 months (control period). During the control period neither physician nor patient knew which were inert and which were reserpine tablets; the tablets were identical in appearance.

All blood pressure readings were made by the same physician. Three readings were taken during each clinical interview, according to a set routine which included a period of rest and the lowest of the three readings was used in the assessment of results. By this means it was hoped to obtain a figure approximate to the resting blood pressure. Blood pressures were taken in sitting, standing, and supine positions for the first six months of the observation and treatment periods, but as there was no material difference between the values obtained this procedure was replaced later by three blood pressures taken in the sitting position. Blood pressure readings were also made on 20 patients at 15-minute intervals for a period of two hours, whilst they were receiving control medication or reserpine, in order to determine whether there was any difference between the lowest reading obtained and that obtained by the lowest of three readings, using a fixed routine. Although the blood pressure fluctuated over the two-hour period there was no material difference in the lowest reading taken by that method and the lowest of a set of three.

Symptoms were assessed at regular intervals throughout the trial. A comprehensive list of possible symptoms was tabulated during the planning of the trial and whether a patient was suffering from these or other symptoms was decided by means of indirect questioning. Questions on the number of colds contracted by a patient, his approach to work or recreation were posed at regular intervals with the intention of determining whether the patient had nasal congestion, lack of initiative, or other adverse effects from the treatment.

Results

Effect on Blood Pressure. The effect of reserpine on the blood pressure in individual patients was tabulated and a summary of the effect on all patients is shown in Table I, which gives the change in blood pressure during the " observation " as compared with the " therapeutic " period.

TABLE I

A Comparison of the Mean Blood Pressure for all Patients in the Observation, Therapeutic, and Control Periods

		No. of Patients	Mean B.P. in			Difference between (B) and (A)	Difference between (C) and (B)
			Observation period (A)	Therapeutic period (B)	Control period (C)		
Group 1	Systolic	16	210	195	193	−15** (t=−4·07, d.f.=15)	−2* (t=1·3 d.f. = 15)
	Diastolic	16	125	111	111	−14*** (t=−5·09, d.f.=15)	−0·25* (t= −0·2, d.f.=15)
Group 2	Systolic	18	213	194	209	−19*** (t= −4·46,d.f.=17)	+15*** (t=5·11, d.f. =17)
	Diastolic	18	124	108	119	−16*** (t= −6·49,d.f.=17)	+11*** (t=4·9, d.f.=17)

* p <0·2. ** p <0·01. *** p <0·001.

Changes in Symptoms during the Observation, Therapeutic, and Control Periods. All symptoms found in patients during observation, therapeutic, and control periods were recorded and the following changes were observed: about one-third described a feeling of calmness or wellbeing during reserpine therapy, but the advantage of this was partly offset by a feeling of tiredness, loss of energy, lack of initiative and depression, in an approximately equal number of patients. A gain in appetite and weight, nasal congestion and nightmares were commonly complained of during treatment. Although anginal and præcordial pain showed no change in frequency during the trial, the

intensity appeared less. The frequency of headaches decreased during the observation period, and further during reserpine therapy. Other symptoms remained largely unaltered.

The most troublesome side-effects were tiredness and nasal congestion, and the most serious was depression. One patient who was excluded from the analysis of results developed extreme depression after three months' therapy.

Case Record 101. A man of 54 had a blood pressure of 180/110 consistently during the observation period, and his behaviour was normal. The patient stated that he had never previously had a period of depression, nor psychiatric treatment. After receiving reserpine 1 mg. daily for 12 weeks he complained of depression. He continued with treatment for a further week, during which time the depression increased, and he became worried regarding the possibility of his having cancer. Treatment was discontinued and he was reassured. It was pointed out to him that his weight was increasing and a number of examinations were performed to convince him that his complaint was not cancer. For the next two weeks, according to his wife, he cried continually day and night, slept little, and on two occasions sent for his family doctor during the early hours of the morning. He was reassured repeatedly by his wife, who was a nurse, and by his family doctor, but it was impossible to placate him. After a further week (three weeks without therapy) his behaviour was normal and he stated he felt fit to start work again.

Effects on Retina, Electrocardiogram, and X-ray Appearances. No changes were found which could be attributed to the reserpine.

Effect on Pulse Rate. The pulse rate was slowed in all the patients during reserpine therapy. The mean reduction was 15 (range 3 to 32). There was no relationship between the changes in blood pressure and the reduction in the pulse rate.

Discussion

In view of the delayed effect of reserpine therapy and the occurrence of spontaneous variations in the blood pressure, it was felt that a test of statistical significance should be applied to determine whether the results could be attributed to chance. Comparison of the differences in mean blood pressure for all patients in the therapeutic and observation periods (Table I) shows that the possibilities of the results occurring by chance were less than 1 in 100 for the systolic pressure in Group 1, and less than 1 in 1000 for the diastolic pressure in Group 1, and for the systolic and diastolic pressures in Group 2. In Group 1 where reserpine was administered in both control and therapeutic periods, p was greater than 0·2 for the systolic and greater than 0·8 for the diastolic. This may therefore be considered as a chance variation. In Group 2 (in which inert tablets were administered in the control period) the difference between the control and therapeutic periods in regard to the systolic and diastolic pressures was such that the possibility of this being a chance finding were less than 1 in 1000.

The average reduction in the blood pressure following reserpine for all 34 patients was 18 mm. Hg in the systolic and 15 mm. in the diastolic when the findings for the observation and therapeutic periods are compared. Approximately 40 per cent of patients showed a reduction of 20 mm. Hg or over in the systolic and diastolic pressures (Table II). These findings agree substantially with those of other workers. Hughes *et al.* (1954) treated 62 unselected hypertensive patients with an average daily dose of 3 or 4 mg. of reserpine. Thirty-three showed a fall in blood pressure of over 20 mm. Hg in both the systolic and diastolic pressures. Of 28 cases with a diastolic pressure between 100 and 120 mm. before treatment, 13 showed an average mean fall in systolic pressure of 29 mm. Hg and 18 mm. Hg in diastolic pressure. In the 15 cases that did not respond the average mean fall in systolic and diastolic pressures was only 8 mm. Hg. Of a second group of 34 patients having diastolic pressure of over 120 mm. of mercury, 20 responded favourably, the average mean fall being from 220/132 mm. to 193/108 mm. Hg, while the remaining 14 cases showed practically no change in the blood pressure. A beneficial effect following the use of reserpine was noted by Hensler (1953) in 13 of 18 cases of essential hypertension, whilst 3 of 13 other non-renal cases showed hypotensive changes. Doyle and Smirk (1954) used 6 to 9 mg. of reserpine daily, and

TABLE II

SUMMARY OF RESPONSE OF THIRTY-FOUR PATIENTS TO RESERPINE

Pressure response (mm. Hg)	Number of patients showing change in systolic pressure		Number of patients showing change in diastolic pressure	
No change (+10 to −9)	11	20	8	19
−10 to −19	9		11	
−20 to −29	8	14	13	15
−30 to −39	2		2	
over −40	4			

found considerable falls of both systolic and diastolic blood pressures which occurred in the first or second day of treatment, and often persisted for 24 hours after treatment ceased. Wilkins *et al.* (1954) found that the average blood pressure of 58 cases of hypertension fell from 191/109 before treatment to 167/94 after treatment.

Tolerance to the hypotensive effect of reserpine did not develop. This can be seen in Fig. 2, in which the blood pressure changes of a patient are shown over a period of two years. This sustained action is also demonstrated by the fact that although the average blood pressure rose almost to the level found in the observation period for those patients receiving inert tablets in the control period, little change was found in the mean blood pressure between the therapeutic and control periods of those receiving reserpine tablets in both. It would seem, therefore, that little tolerance occurs in the period of 12 to 18 months' continuous reserpine therapy.

Side-effects, particularly lack of initiative, tiredness, and lack of vitality, occurred to a degree that would make reserpine therapy unsuitable for continuous administration in some patients. Only one severe case of depression was found in this series. No tolerance of these side-effects developed after the first two weeks of therapy in which tiredness was a common symptom.

It may be concluded that reserpine is a valuable drug in the treatment of some cases of hypertension. It has the advantage of having a less violent and more prolonged action than hexamethonium and tolerance does not seem to develop on continuous administration. Adverse features are that it does not act in all patients, and that its hypotensive effect is relatively small. While side-effects are not marked, care must be taken not to make the life of patients miserable because of lack of vitality in return for the unproven value of reducing the blood pressure. The physician must be on the alert for the onset of extreme depression and mental disturbance.

SUMMARY

Reserpine in a dose of one to two mg. daily was administered to 34 hypertensive patients for a period of twelve to eighteen months. One additional patient was not considered in the results as therapy had to be stopped after three months owing to the onset of extreme depression.

Approximately 40 per cent of patients showed a hypotensive effect of over 20 mm. Hg. The average reduction in the blood pressure for all patients was 18/15 mm. Hg.

No tolerance to the hypotensive effect of reserpine was noted over a period of twelve to eighteen months. Side-effects such as lack of initiative and tiredness may make reserpine unsuitable for indefinite administration in some patients. The physician must watch for the possible development of depression or other mental disturbances in some patients.

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CARDIAC AMYLOIDOSIS

BY

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Although Wilks (1856) originally postulated the existence of a form of lardaceous disease that appeared to be the primary affection, it was not until 1939 that the features of primary systemic amyloidosis were fully reviewed by Koletsky and Stecher. The disease is less rare than is generally supposed. Thus, only ten cases had been reported in 1930, whereas the number had risen to 48 in 1945, and to 71 in 1950. This implies a growing awareness of a disease that has hitherto received but little attention in this country. Wild (1886) mentioned cardiac failure in primary amyloidosis but it was Lindsay (1946) who emphasized its common occurrence. Heart failure was present in 56 per cent of 71 cases reviewed by Higgins and Higgins (1950) and this is now accepted as the most important single feature.

The object of this paper is to describe the clinical and pathological findings in five cases of primary amyloidosis presenting with cardiac symptoms, and to direct attention to the disease as a cause of heart failure.

Case Reports

Case 1. A woman, aged 54, was admitted to hospital with a history of progressive dyspnœa on exertion during the past four years, latterly with swelling of the legs and abdomen. There was severe heart failure with orthopnœa, gross œdema of the legs, a raised venous pressure, liver enlargement, and ascites. Triple rhythm was noted and there were no murmurs. Radiologically there was pulmonary congestion with moderate generalized cardiac enlargement (Fig. 1). The electrocardiogram was of low voltage with a diphasic T wave in leads I and CR7 (Fig. 2). Treatment with fluid and salt restriction, digitalis, and mercurial diuretics resulted in some improvement, and after a month she was discharged to attend as an out-patient. Nine months later she was readmitted with tense œdema extending to the lower abdominal wall. As before, there were no murmurs and a faint third heart sound was present. The blood pressure was 140/90 mm. Hg. Radiologically, pulmonary congestion was now more advanced and a small right hydrothorax had developed. The arm-to-tongue circulation time (saccharin method) was prolonged to 41 seconds. The urine contained about one-tenth volume of albumin* on most occasions. Renal and liver function tests were normal. Complete blood counts were also normal. The serum protein level was 5·5 g. per 100 ml. with some reduction in the albumin fraction (albumin 2·7 grams, globulin 2·8 grams). During the third and fourth weeks the pulse was observed to be irregular from auricular fibrillation, but the rhythm subsequently returned to normal. Nearly two months after admission there was still massive œdema of the legs with a moderate right hydrothorax. Acupuncture gave partial relief on two occasions with yields of 21 and 12 pints respectively, but her general condition remained stationary and she was eventually discharged home after a stay of three months. Three weeks later she was admitted for the third time. Massive œdema had spread to involve the breasts and upper extremities, and on the following day she became more breathless and died in coma.

* The volume occupied by the albumin when the whole quantity of acidified urine has been boiled and allowed to settle.

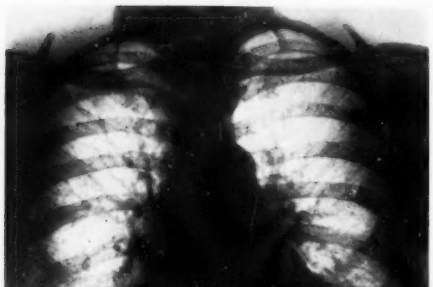

FIG. 1.—Case 1. Teleradiogram showing moderate generalized enlargement of the heart with pulmonary congestion.

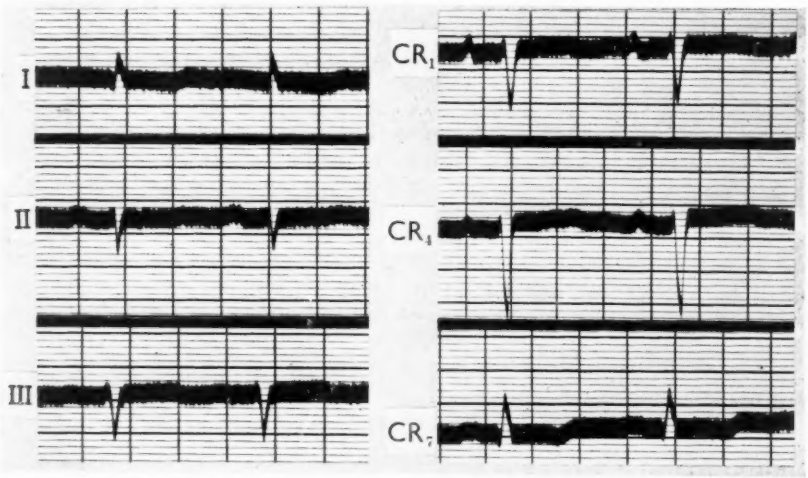

FIG. 2.—Case 1. Low voltage electrocardiogram with diphasic T wave in leads I and CR7.

Summary of Necropsy (P.M. 226/47)—*Heart Failure. Primary Atypical Amyloid Disease*

Heart—Slight fibrous thickening of visceral pericardium, extensive over right heart, more patchy over left heart. Hypertrophy and dilatation of right ventricle (0·5 cm. thick), slight of rubbery grey myocardium of left atrium but none of abnormally firm mottled red and brown myocardium of left ventricle. Smooth grey thickening of endocardium of left atrium, slight of right atrium. Recent antemortem thrombus in left auricular appendage. Valves normal. Moderate general atheroma.

Other Organs—Partial collapse of lower lobes of œdematous lungs. Clear straw-coloured pleural effusions (800 ml. each side). Slight induration of tongue. Reticular congestion of liver. One infarct in each congested kidney. Firm congested spleen. Slight ascites (30 ml.). Slight thickening of parietal peritoneum. Red, partly adipose, marrow in upper three-quarters of shaft of femur. Very great pitting œdema of legs, trunk, back, and arms. Weights: heart 396 grams; liver 1300 grams; kidneys 370 grams; spleen 170 grams; body weight 73·4 kg.

Microscopical Examination

Heart—Sections of right and left atria and ventricles, mitral and tricuspid valves and of both main branches of the left coronary artery were examined. Amyloid infiltration is present in the walls of several medium sized and small coronary arteries and in a few capillaries and veins in all the cardiac chambers. It is absent from the walls of the main branches of the left coronary but is present in a few capillaries in their adventitia. It is seen apart from vessels in the myocardium of left and right ventricles, left atrium and to a lesser extent in right atrium. It is conspicuous in epi- and endo-cardium in most sections. In the myocardium it occurs chiefly as irregular plaques (Fig. 3) but in the right ventricle irregular branching threads enclose some muscle fibres in a network. In some of the fibres loss of nuclear staining, loss of striation and vacuolation of cytoplasm indicate necrosis, but the latter is not massive. Patches of amyloid are present in the substance of both mitral and tricuspid valves.

In sections of tongue and pharynx the amyloid appears both in the submucosa and between muscle fibres; it is also seen in the latter site in bladder, diaphragm, and psoas muscle. In these organs and also in the broad ligament, ileum, pectoral muscle, liver, spleen, kidney, and lungs infiltration of the walls of

FIG. 3.—Case 1. Amyloid plaques between muscle fibres of left auricle. Crystal violet; × 220 approx.

vessels is conspicuous. These are mostly vessels of small calibre and chiefly arteries and arterioles, although in some sites, e.g. the submucosa of the bladder, small capillaries and venules appear also to be affected. It is difficult to be certain of this as the thickened vessels resemble arterioles but the absence of an internal elastic lamina and the appearance of neighbouring normal vessels suggest that some are capillaries. In the liver, arteries and arterioles of portal systems are involved; in the spleen, central arterioles of Malpighian bodies and in the kidney a few arcuate arteries, interlobulars and a very few vasa afferentia. The presence of renal infarction (presumably embolic) is confirmed but no evidence of necrosis is present in the other tissues. In the lung several bronchial and a few small pulmonary arteries are infiltrated but in only two of these is there intimal cellular proliferation. The tissues mentioned were the only ones examined except for the aorta and main pulmonary artery. In these amyloid is confined to small arterioles and capillaries in the adventitia.

Case 2. A five-year history of ill health in a woman, aged 62, began with episodes of palpitation and breathlessness associated with retrosternal pain and vomiting. On account of these symptoms she was twice admitted to another hospital, and on one occasion the electrocardiogram showed complete heart block with subsequent return to normal rhythm. For three months before her admission to hospital she had been confined to bed with dyspnœa, recurrent chest pain, and persistent heart irregularity. The signs were those of heart failure but without œdema. There were no murmurs and the blood pressure was 105/80 mm. Hg. An electrocardiogram showed auricular tachycardia with 2 : 1 A-V dissociation (Fig. 4A). Auricular fibrillation was induced with digitalis (Fig. 4B), and normal rhythm was restored within four days (Fig. 4C). She left hospital a month later on a maintenance dose of quinidine. Three years later she was again admitted complaining of occasional palpitation and increasing breathlessness. There was still no œdema, but the venous pressure was raised, the liver was distended and crepitations were present at the lung bases. The appearance of the tongue was normal. Triple rhythm was well heard at the apex, and there were no murmurs. There was no albuminuria, and the blood pressure was 130/85 mm. Hg. The hæmoglobin was 85 per cent and the blood count was otherwise normal. Plasma proteins were not estimated. Radiologically there was considerable generalized cardiac enlargement with

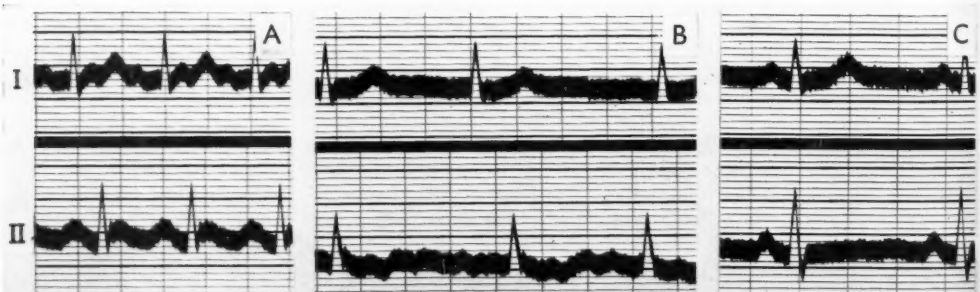

FIG. 4.—Case 2. The electrocardiogram in (A) is of moderately low voltage and shows auricular tachycardia with 2 : 1 A-V dissociation; (B) recorded 13 days later shows auricular fibrillation, and sinus rhythm returned (C) four days after withdrawal of digitalis.

pulmonary congestion (Fig. 5). The electrocardiogram was of low voltage with the T wave inverted in lead III and flattened in leads II and CR7 (Fig. 6). There was a limited response to treatment and on discharge one month later she was still moderately dyspnœic. Within three months she was again admitted with progressively severe dyspnœa aggravated two weeks previously by pulmonary infarction. The electrocardiogram now showed established auricular fibrillation with right bundle-branch block (Fig. 7). A few days later a secondary pulmonary infarct occurred from deep vein thrombosis in the left calf. Treatment was begun immediately with heparin and dicoumarol, the prothrombin index being estimated daily. On the eighteenth day diffuse skin ecchymoses appeared with the prothrombin index at 50 per cent. Anticoagulants were stopped and large doses of vitamin K were given, but the prothrombin index fell to 28 per cent. On the following morning she was found to have a left hemiplegia which proved fatal within a few hours.

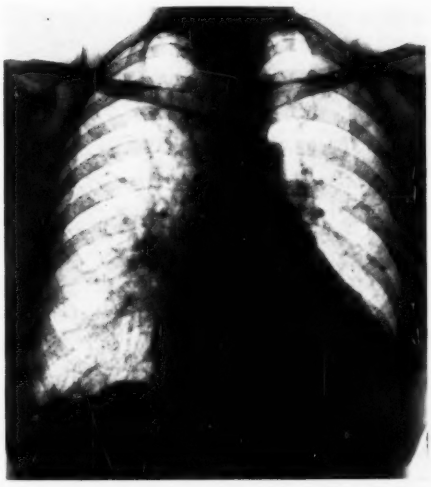

FIG. 5.—Case 2. Teleradiogram showing considerable generalized enlargement of the heart with pulmonary congestion.

Summary of Necropsy (P.M. 435/47)—*Cerebral Hæmorrhage and scattered hæmorrhages throughout body. Dicoumarol therapy. Heart Failure. Primary Idiopathic Amyloid Disease*

Heart—Recent fibrinous pericarditis with some associated petechiæ. Generalized cardiac enlargement, most pronounced in the upper posterolateral half of the left ventricle where an area, up to 2·5 cm. thick, with a waxy appearance of grey interlacing strands between brown muscle was fairly sharply circumscribed. Remainder of left ventricle relatively flabby with a few faint grey areas on the mostly uniform brown cut surface. Moderate hypertrophy of right ventricle and of both atria. Grey thickening of endocardium of both atria and slight of mitral and tricuspid valves; slight granularity of the auricular aspect of the mitral cusps and the thickening of the tricuspid most marked in an area (1 cm. diam.) on right anterior cusp. Aortic and pulmonary valves normal. Moderate general atheroma of systemic arteries but slight in coronary arteries.

Other Organs—Recent infarct in right lung; collapse of lower lobe of left lung. Blood-stained effusion (295 ml.) in left pleural cavity. Extensive hæmorrhage in left cerebrum communicating with lateral ventricle. No visible abnormality in main cerebral arteries. Infarct in left kidney. Hæmorrhage in perirenal and retrocolic tissue. Reticular back-pressure congestion of liver with focal atrophy and regeneration.

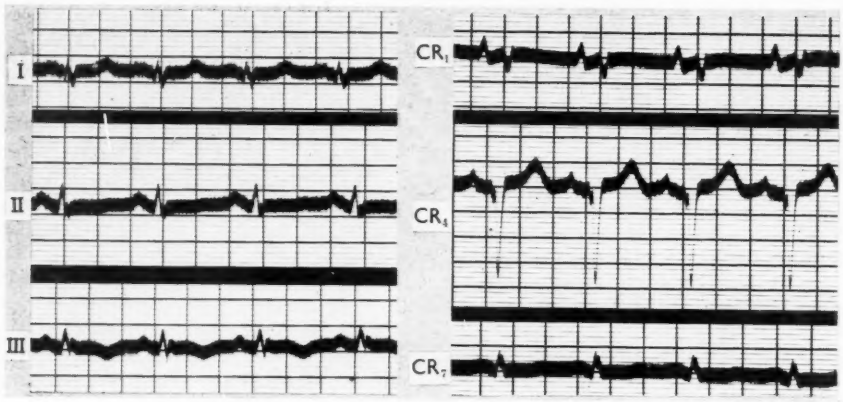

FIG. 6.—Case 2. Low voltage electrocardiogram with the T wave inverted in lead III and flattened in leads II and CR7. The patient was not receiving digitalis.

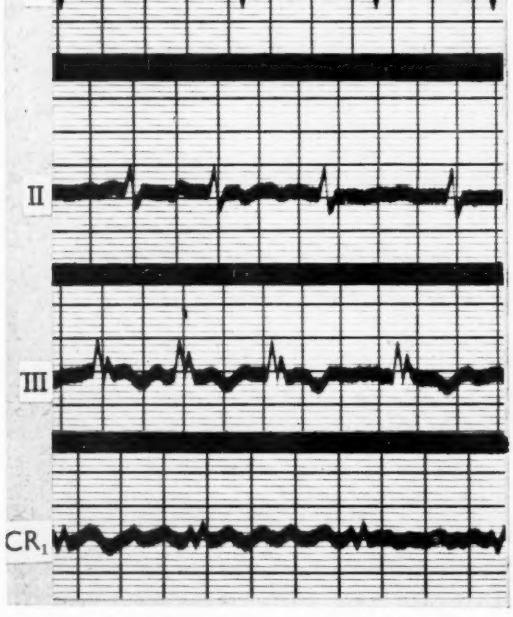

FIG. 7.—Case 2. Electrocardiogram showing established auricular fibrillation with right bundle-branch block.

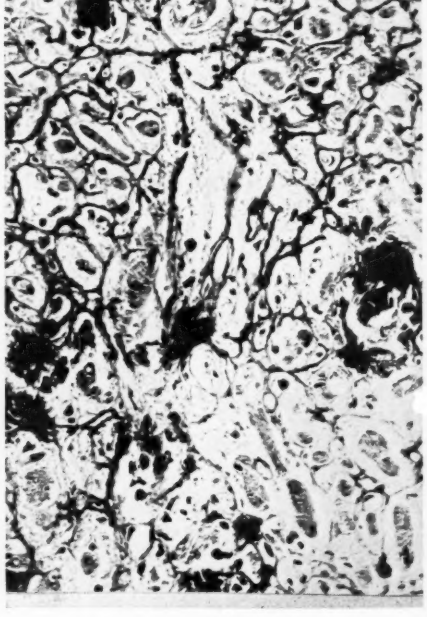

FIG. 8.—Case 2. Amyloid network enclosing partly necrotic muscle fibres of left ventricle. Congo red; × 230.

Normal tongue. Red marrow throughout vertebrae, in sternum and in patches in upper third of shaft of femur. Numerous ecchymoses in subcutis. Œdema of legs and sacral pad. Slightly wasted woman. Weights: heart 532 grams; liver 1332 grams; spleen 106 grams; kidneys 205 grams; body weight 50·4 kg.

Microscopical Examination

Heart—Sections from all four cardiac chambers and mitral and tricuspid valves were examined. Amyloid is present as focal patches in the media of many medium-sized and small arteries, and in a few veins and capillaries in epi- and myocardium. From some of the vessels it extends as irregular plaques into surrounding connective tissue, separating muscle bundles. In the upper half of the posterolateral wall of the left ventricle (the area most striking to the naked eye) the amyloid forms an irregular net of fine and coarse strands which in some areas enclose muscle fibres (Fig. 8). Plaques of amyloid are present not only in this area but also in the fibrotic endocardium, the epicardium over the left atrium, and the substance of the mitral and tricuspid valves. Necrosis of many muscle fibres enclosed by the amyloid strands is indicated by loss of nuclear staining, loss of striation, and vacuolation of cytoplasm. Such necrosis is patchy and is not associated with inflammatory reaction. The only trace of the latter is an occasional foreign body giant cell accompanied by scanty lymphocytes and spindle fibroblasts around a few amyloid plaques.

Amyloid appears in the submucosa of the tongue and in minute areas in the perineurium of the sciatic nerve. In these tissues, and also in the spleen, liver, bladder, kidney, mesentery, psoas muscle, diaphragm, uterus, suprarenal, pancreas, and lung, amyloid infiltrates the walls of bloodvessels. Small and medium sized arteries are commonly involved, veins and capillaries rarely. In the kidney, arcuate and interlobular arteries are affected; in the liver, the arterioles of the portal systems, and in the spleen the central arterioles of the Malpighian bodies. Small focal plaques of amyloid are seen in the media of a main branch of a pulmonary artery within the lung and in several other arteries of all sizes in both lungs. This is associated with intimal cellular proliferation in only a very few. The only sections examined which showed no trace of amyloid were of cerebellum, frontal cortex, and bone marrow. There is no evidence of plasma cell proliferation either in the latter or in the spleen.

Case 3. A woman, aged 57, was admitted to hospital with a history of gradually progressive dyspnœa for one year and intermittent swelling of the ankles for five weeks. Two days before admission she had a severe episode of palpitation and dyspnœa lasting an hour followed by persistent vomiting. At first her general condition was fair. There was no œdema, but the neck veins were distended, the liver was easily palpable and crepitations were present at both lung bases. The pulse was regular, and the blood pressure was 110/70 mm. Hg. The apex beat was displaced 2·5 cm. to the left, and there were no murmurs. The hæmoglobin was 80 per cent. The urine had a specific gravity of 1020 and contained one-fifth volume of albumin. A renal factor was suspected, and this was later confirmed histologically. Undoubted evidence of heart failure soon appeared, however, with gradually increasing dyspnœa and œdema. Energetic treatment with digitalis and mercurial diuretics produced little improvement, although the blood urea which had been 99 mg. per 100 ml. on admission fell to normal during the seventh week. At the time of her death during the tenth week extensive anasarca of the lower extremities had spread to involve the abdominal wall. Neither a chest X-ray nor an electrocardiogram are available to complete the details of this patient, but the general clinical picture was that of severe and progressive heart failure.

Summary of Necropsy (P.M. 294/35)—*Heart Failure. Primary Idiopathic Amyloid Disease*

Heart—Slight diffuse fibrous thickening of pericardium. Tough dry myocardium. Considerable dilatation and moderate hypertrophy of right ventricle (R.V. 0·4 cm., L.V. 1·5 cm.). Great dilatation of right atrium, less of left. Moderate atheroma.

Other Organs—Congestion of liver. Moderate enlargement of hard, rubbery spleen with loss of pattern on flat, dry cut surface. Slightly enlarged firm kidneys. Œdema and congestion of lungs. Multiple serous effusions with coagula (ascites 590 ml.; left pleura 60 ml.; right pleura 180 ml.; pericardium 30 ml.). Brownish red, partly adipose marrow in neck and upper two-thirds of shaft of femur. Slight jaundice of skin and of conjunctivæ. Gross pitting œdema of legs and thighs. Weights: heart 368 grams; liver 2411 grams; kidneys 368 grams; spleen 255 grams; body weight 55·8 kg.

Microscopical Examination

Heart—Only the right and left ventricles were examined. These show widespread deposition of amyloid between muscle fibres, chiefly as patches but in places as irregular strands. Plaques are frequent in the walls of the smaller coronary vessels and in a few are associated with an adjacent intimal proliferation which narrows the lumen considerably. Some diffuse fibrosis of the myocardium is associated with these changes and in a frozen section of the left ventricle there are numerous fine sudanophil droplets in the muscle fibres.

Other Organs—In the kidney small deposits of amyloid are present in about a third of the glomerular tufts, in a few vasa afferentia and interlobular arteries, in several arcuate arteries and a few vasa recta. Widespread parenchymatous and some fatty degeneration affects the tubules of the cortex; hyaline droplet change is seen in a few. Hyaline, granular and a few fatty casts are present in their lumina. The spleen is extensively infiltrated by amyloid. Sinuses are still evident, but no other trace of a pattern is left and only small groups of lymphocytes are scattered in the hyaline amyloid background. In the stomach and jejunum amyloid replaces some muscle fibres and is present in the small arteries of the submucosa. In the suprarenal it is restricted to similar vessels in the capsule, and in the liver to the arterioles of the portal system.

Severe reticular congestion is present in the liver, together with central atrophy of lobules, extensive fatty change of parenchyma and some regeneration as indicated by numerous binucleate cells. The only other organs examined were the upper lobe of the right lung which is free from amyloid and the pancreas where only a very few small arteries are infiltrated.

Case 4. A woman, aged 46, was admitted to hospital because of progressive breathlessness for five months followed by swelling of the ankles. On examination, the feet were not swollen but there was moderate pitting œdema in the sacral area. The neck veins were slightly distended, the liver edge was palpable four fingers' breadth below the costal margin and there were signs of pulmonary congestion with a small right hydrothorax. The pulse was regular and the blood pressure was 130/90 mm. Hg. There were no murmurs. The apical second sound was recorded as being noticeably split. The tongue and fauces appeared normal. The urine was normal. The electrocardiogram showed right bundle-branch block with moderately low-voltage complexes, and a short Q wave in leads I and CR4 was indicative of anterior cardiac infarction (Fig. 9). Radiologically there was considerable generalized cardiac enlargement with a small hydrothorax on the right side. On fluoroscopy the pulsation of the heart was greatly diminished, and this accounted for the stencilled cardiac outline in the X-ray film (Fig. 10). There was no evidence of pericardial calcification. A complete blood count, E.S.R. and a full range of liver function tests gave normal results. Although the heart was enlarged and pericardial calcification was absent, the association of a quiet heart on fluoroscopy with distension of the liver and neck veins suggested constrictive pericardial disease. A period of treatment with digitalis, mercurial diuretics, and a restricted intake of fluids and sodium was observed before deciding upon operation. These measures met with no success. The pleural effusion required aspiration on two occasions, and when she left hospital after a stay of four months her condition was unchanged. Although confined to bed under the care of her own doctor she became increasingly breathless and was re-admitted six months later. She was by now slightly cyanosed and there was considerable œdema of the legs and sacral area. The liver edge was palpable five fingers' breadth below the costal margin and there was evidence of ascites. Moist crepitations were heard in both lungs and there were signs of a large pleural effusion on the right side. X-rays showed that a smaller effusion was also present on the left side. There were no murmurs, and the electrocardiogram showed no further change from the previous tracing. With the patient supine the venous pressure measured at the arm was 17 cm. saline above the sternal angle. Blood counts and liver-function tests were normal as before. The serum protein level was 6·5 g. per 100 ml. (albumin 4·0 grams, globulin 2·5 grams). In spite of the conflicting evidence afforded by the chest X-ray and electrocardiogram, constrictive pericardial disease was still thought to be the most likely diagnosis. It was therefore decided to submit the patient to thoracotomy. At operation, however, the pericardium presented a normal appearance and subsequent examination of biopsy material was negative. There was considerable enlargement of the heart as a whole, and its range of movements was observed to be greatly diminished. In the days

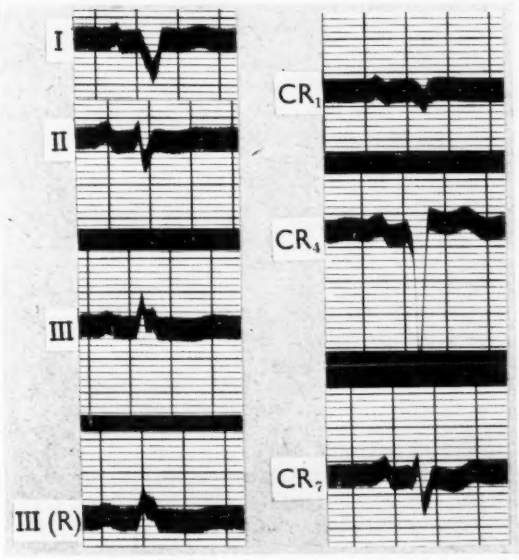

FIG. 9.—Case 4. Moderately low voltage electrocardiogram with right bundle-branch block. A short Q wave in leads I and CR4 suggests anterior cardiac infarction. The patient was receiving digitalis.

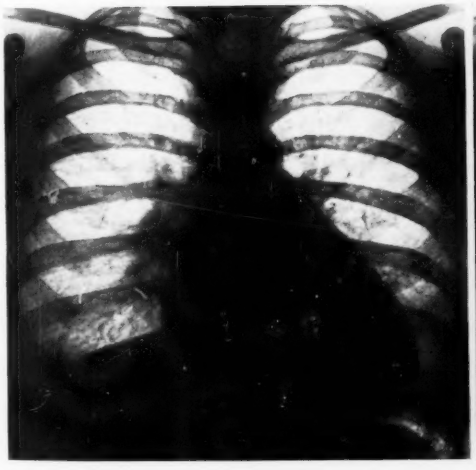

FIG. 10.—Case 4. Teleradiogram showing considerable generalized cardiac enlargement with pulmonary congestion and a small hydrothorax. The outline of the heart has a stencilled appearance which is due to greatly diminished cardiac pulsation.

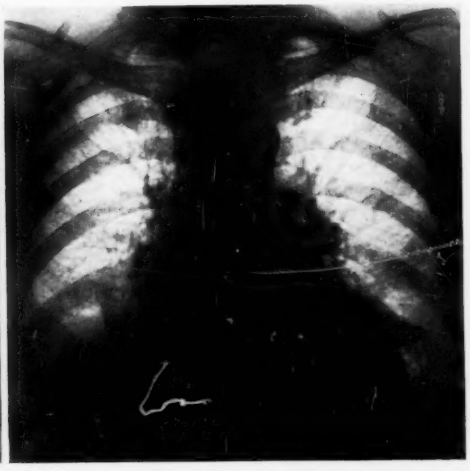

FIG. 11.—Case 5. Teleradiogram showing moderate cardiac enlargement with pulmonary congestion and a small hydrothorax.

which followed her condition steadily worsened and became further complicated by venous thrombosis arising in the right leg. She died suddenly from pulmonary embolism on the seventeenth day after the operation.

Summary of Necropsy (P.M. 58/51)—*Pulmonary Embolism. Chronic Heart Failure. Primary Idiopathic Amyloid Disease. Recent Operation—Pericardotomy*

Antemortem thrombus (10 cm. long and up to 1·5 cm. diam.) in main pulmonary artery. Similar thrombus in right femoral vein.

Heart—Partly organized fibrinous exudate loosely uniting visceral and parietal pericardium. Operative defect (5 × 2·5 cm.) in left side of parietal pericardium. Diffuse hypertrophy of myocardium of whole heart but more obvious in ventricles (L.V., 1·8 cm.; R.V., 0·8 cm. thick). Antemortem thrombus in auricular appendages. Irregular area of yellow necrosis, approximately 4 cm. from above down and 1–1·5 cm. diam. surrounded by grey, glistening zone, up to 0·8 cm. thick, in upper half of lateral wall of left ventricle. Firm, red myocardium elsewhere. Patches of greyish-white subendocardial fibrosis in both auricles, none in ventricles. No fibrosis of pericardium. Very slight thickening of free edge of junction of anterior and posterior cusps of mitral; remaining valves normal. Slight atheroma.

Other organs—Reticular congestion of liver. Firm congested spleen. Congested kidneys. Hæmorrhagic infarcts in congested lungs. Patches of fibrinous exudate over pleura of both lungs. Clear brown pleural effusions (1050 ml. right, 60 ml. left); clear fluid (360 ml.) in peritoneal cavity. Brick red, partly adipose marrow in upper 21 cm. of 34-cm. shaft of femur; similar marrow in sternum. Well-healed scar, 30 cm. long, in skin over left side of chest. Œdema of right leg, slight of left. Slightly wasted woman. Weights: heart 610 grams; liver 1644 grams; kidneys 360 grams; spleen 135 grams; body weight 51·8 kg.

Microscopical Examination

Heart—In this example the most striking feature is the area of necrosis in the left ventricle. Muscle fibres in which nuclei have disappeared, but in which longitudinal striation is still present, are conspicuous. These blend imperceptibly with an ill-defined eosinophil matrix in which the only suggestion of structure is an occasional vessel and some longitudinal strands. It is possible that the latter represent collapsed sarcolemmal sheaths. This matrix fails completely to react with stains for amyloid and collagen although the walls of small vessels in and about it are positive to Congo red. It is therefore interpreted as complete necrosis, and the adjacent area with some residual striation in fibres as a zone of partial necrosis. Although no thrombus was detected in any major coronary vessel at necropsy, many of the smaller arteries and veins, with amyloid deposited in their walls, show intimal cellular proliferation with great reduction of their lumina. It appears that ischæmia from this stenosis of small vessels is the cause of the necrosis. A surprising feature is the extremely scanty inflammatory reaction in and around the necrosis; it is represented by a very few small collections of polymorphonuclear and mononuclear cells. These findings suggest that the ischæmia was relatively slow, and provide a possible explanation for the absence of cardiac pain. Apart from this area, amyloid is conspicuous in the walls of small arteries and veins in all cardiac chambers, but is less extensive outside vessels than in Cases 1, 2, and 3. There are a few small patches in the substance of the mitral valve.

Elsewhere, amyloid is present as scanty patches between the muscle fibres of the tongue, in its submucosa, and as rings around the basement membranes of acini of mucous glands. In the stomach there are irregular patches in the deep part of the mucosa. In the pancreas there is extensive infiltration between lobules, and the walls of vessels are affected more severely than in the tongue and stomach. Infiltration is restricted to vessel walls in the body of the uterus, lungs, kidney, suprarenals, bladder, psoas muscle, ileum, mesentery, liver, and spleen. Arteries are affected more frequently than veins or capillaries. The only tissues examined in which amyloid is not found are the cerebellum, pituitary, a lymph gland, and bone marrow. There is no unusual plasma cell proliferation in either of the two latter tissues or in the spleen. Other findings are conspicuous central congestion of the liver and hæmorrhagic infarction in the lung.

Case 5. A woman, aged 63, was admitted to hospital with a history of progressive breathlessness, intermittent ankle œdema, and epigastric discomfort over the past year. Latterly the œdema had extended to the knees and dyspnœa had become severe. On examination there was slight

cyanosis, pitting œdema of the legs and sacral area, distension of the neck veins, evidence of pulmonary congestion and slight enlargement of the liver. The pulse was regular and the blood pressure 110/70 mm. Hg. The heart sounds were distant and there were no murmurs. The tongue presented a normal appearance apart from some anterior fissuring. The urine contained one-fifth volume of albumin and the specific gravity was 1015. A differential blood count was normal and the hæmoglobin was 85 per cent. The serum protein level was 5·2 g. per 100 ml. X-rays showed that there was moderate cardiac enlargement with pulmonary congestion and a small right hydrothorax (Fig. 11). An electrocardiogram was not recorded. Renal function tests soon after admission showed a marked diminution in P.S.P. excretion, and although the blood urea was found to be only 45 mg. per 100 ml. the heart failure was thought to be secondary to chronic nephritis. Treatment with digitalis, however, resulted in the disappearance of œdema, reduction of albuminuria to a faint haze and improvement in P.S.P. excretion to 53 per cent in two hours. The diagnosis was amended to one of primary cardiac failure, and after five weeks the patient was discharged from hospital. Her breathlessness and œdema gradually returned, and three months later a violent attack of dyspnœa with collapse led to her urgent readmission. She died twelve hours later.

Summary of Necropsy (P.M. 44/47)—*Heart Failure. Primary Atypical Amyloid Disease*

Heart—Considerable hypertrophy of ventricles: L.V., 2 cm.; R.V., 0·7 cm. thick; and of left atrium, 0·4 cm. thick. (No note of the texture of the myocardium or of the pericardium or endocardium was made at necropsy: the diagnosis was made only on histological examination.) Moderate general atheroma.

FIG. 12.—Case 5. Amyloid in media of small coronary artery; œdematous thickening of the intima with scanty amyloid. Verhoff; × 200. (The dark areas react positively in a Congo red stain.)

FIG. 13.—Case 5. Small pulmonary artery. Amyloid in media and intima. Œdematous thickening of intima with considerable reduction of lumen. Congo red; × 195.

Other organs—Clear pleural effusions (1950 ml. right, 1240 ml. left). Congestion of rather dry, poorly aerated lungs. Collapse of lower half of left lower lobe, lower and anterior angle of left upper lobe, lower half of right lower lobe, the whole of the right middle lobe and lower and anterior third of right upper lobe. Reticular congestion of liver. Congestion of spleen. A few small pits of ischæmic atrophy on very faintly granular surface of congested kidneys. Fibrous adhesions about liver and spleen. A few patches of red, fatty marrow in upper half of shaft and neck of femur. Œdema of lumbar region and ankles. Well-nourished woman. Weights: heart 645 grams; liver 1815 grams; kidneys 404 grams; spleen 200 grams; body weight 60 kg.

Microscopical Examination

This was limited to the right and left ventricles, the lower lobe of the right lung, the right kidney and the right radial artery.

Heart—Amyloid infiltration is present in the walls of several smaller coronary arteries and veins. In a few of the infiltrated arteries there is a further œdematous thickening of the intima with considerable reduction of their lumina (Fig. 12). Amyloid is nearly always absent in such an intima; collagen fibrils and cells are also extremely scanty. Apart from the vessels amyloid is not extensive in the myocardium, but a few plaques and a few irregular strands are present. There is, however, no evidence of necrosis of muscle fibres. In the single *lung* section available amyloid infiltration is extensive. It affects the walls of many arteries and veins, and small patches are present in several alveolar capillaries. In affected arteries, the deposit is usually in the media, and is conspicuous adjacent to the internal elastic lamina. It may, however, extend focally into the intima, and in some vessels the elastic is partly destroyed so that the localization of the infiltration is difficult. Many of the infiltrated arteries have a further œdematous thickening of the intima in which only a few fibroblasts or small round cells are present, similar to that seen in coronary arteries and producing stenosis (Fig. 13). The lung parenchyma is collapsed.

In the kidney amyloid is present in several arcuate and interlobular arteries and in vasa afferentia but not in vasa recta. About half of the glomeruli show small focal deposits similar to those seen in Case 3, but the extensive infiltration and obliteration of glomerular tufts so common in secondary amyloidosis is not seen. Parenchymatous degeneration of tubules is widespread and several contain hyaline casts.

Discussion

Primary amyloidosis is said to differ from the more commonly encountered secondary form in that deposits are found chiefly in cardiac, skeletal, and smooth muscle, and only very slightly in the liver, spleen, kidneys, and adrenals. Although occasional overlap in distribution between the two forms shows that this distinction is not strictly valid, it is only in primary amyloidosis that the heart may be chiefly affected. Since routine post-mortem examination may fail to yield the correct diagnosis, we believe the disease to be less rare than would appear from a study of previously reported cases.

The recorded *age distribution* lies between 24 and 90 years (Higgins and Higgins, 1950). Most cases occur in the sixth and seventh decades, and in our series the average age at the onset of symptoms was 55 years. This contrasts with the much earlier incidence of secondary amyloidosis. The *sex distribution* is reported to be about equal (Eisen, 1946), but all our patients were women.

Since the primary form of amyloidosis most commonly presents with heart failure, special emphasis is laid on this important aspect of the disease. *Dyspnœa on exertion* was the main complaint of our five patients and it was the initial symptom in all but one (Case 2) who presented with paroxysmal tachycardia. Similarly, *anasarca* was present in all except Case 2 in whom the natural course of the disease was prematurely terminated by cerebral hæmorrhage complicating dicoumarol treatment. Anginal pain was never present, and is almost unknown in cardiac amyloidosis. A variable degree of *generalized cardiac enlargement* was always found, and the average weight of the hearts at necropsy was 510 grams. Cardioscopy showed sufficiently *diminished pulsation of the heart* in one patient (Case 4) to suggest constrictive pericardial disease. Two other cases have been reported in which this diagnosis was made during life, and in one of these a fruitless thoracotomy was similarly undertaken (Findley and Adams, 1948; Couter and Reichert, 1950). *Triple rhythm* was noted in two patients. As in most other reported cases, *murmurs* were conspicuously absent.

Hypotension was present in three patients, and this feature has been emphasized by other authors (Kerwin, 1936; Koletsky and Stecher, 1939; Binford, 1940; Kalbfleisch, 1940; Soisalo and Ritama, 1944; Eisen, 1946; Ranström, 1946; Baber, 1947). *Normal rhythm* was found in four patients, though in one of these a transient phase of auricular fibrillation was observed; in the remaining patient (Case 2) auricular fibrillation became established. An *electrocardiogram* was recorded in three patients, and the tracings were all of low voltage, with a diphasic T wave in leads I and CR7 (Case 1) or right bundle-branch block (Cases 2 and 4). The cardiographic changes in Case 2 deserve special metion because the observed sequence of paroxysmal tachycardia, transient complete heart block, sinus rhythm, and finally established auricular fibrillation with right bundle-branch block has not hitherto been described in cardiac amyloidosis. Case 4 was also quite exceptional in that, in spite of the absence of cardiac pain, a zone of necrosis was found in the lateral wall of the left ventricle at necropsy which accounted for the Q wave in leads I and CR4 of the electrocardiogram. The tracings in previously reported cases have most frequently been of low voltage with normal rhythm and a low, diphasic or inverted T wave in lead I and the left præcordial leads. These changes may sometimes resemble those recorded in ischæmic heart disease, but in their degree and distribution they seldom conform fully to those accompanying heart failure from antecedent cardiac infarction. While differentiation may be impossible, particularly when evidence of infarction is suppressed by bundle-branch block, it is considered that the presence of inadequate changes in the electrocardiogram of a patient with chronic unexplained heart failure should always suggest the possibility of cardiac amyloidosis. Auricular fibrillation and conduction defects have occasionally been described (Larsen, 1930; Josselson and Pruitt, 1953). Disturbances of conduction have been limited for the most part to bundle-branch block, but prolongation of the P–R interval (Dillon and Evans, 1942), 2 : 1 heart block (Götze and Krücke, 1941) and complete heart block (Dahlin and Edwards, 1949; Josselson and Pruitt, 1953) have been noted in a few instances. Examination of the *urine* showed up to one-fifth volume of albumin in three cases, nothing abnormal being found in the remaining two. In contrast to secondary amyloidosis renal involvement in the primary form is usually minimal though present histologically (as in Cases 3 and 5) in about half the reported instances (Lindsay, 1948). A few cases of the " nephrotic syndrome " have been reported, and such a patient having extensive renal and cardiac amyloidosis was omitted from this series since the extreme anasarca was thought to be due to a combination of both factors. *Blood* examination in our patients was usually unrewarding, the average hæmoglobin being 88 per cent. The total serum protein was within physiological limits in the three patients in whom it was evaluated though in two it was at the lower level of normal. The albumin–globulin ratio was estimated in two patients, and in one (Case 1) the albumin fraction was exceeded by the globulin. In his review of 46 cases Eisen (1946) found normal values in the nine instances where the serum protein had been recorded, but considered moderate hypochromic anæmia to be a fairly consistent feature. The *Congo red test* is rarely positive, and this may be due to the fact that as judged by histological examination the amyloid in the primary form has less affinity for this dye than in the secondary form. In addition, the amyloid collectively may be insufficient to give a positive result.

None of our cases exhibited any of the non-cardiac manifestations so often described in the primary form of amyloidosis. Of these the most important is *macroglossia*, the incidence of which is as high as 42 per cent at necropsy (Eisen, 1946). In view of its reported frequency as a prominent and easily recognizable feature it is surprising that Baber (1947), in describing such a case which one of us was fortunate enough to see with her, could find only three previous instances on record in this country (Weber *et al.*, 1937; Barnard *et al.*, 1938). In the present series slight induration of the tongue from amyloid infiltration was noted once at necropsy (Case 1), and it would seem that even in the absence of macroglossia careful palpation of the tongue and adjacent muscles may sometimes yield important information in patients with unexplained heart failure. *Skin deposits* and *purpuric manifestations* are said to occur in about one-quarter of the cases, and this aspect of the disease has been fully reviewed by Goltz (1952). The *lymph glands* are moderately

enlarged in 27 per cent of cases (Higgins and Higgins, 1950), and are involved histologically in 37 per cent (Eisen, 1946). Short of biopsy, however, this feature is of little material help in diagnosis. The *skeletal muscles* are affected histologically in 41 per cent of cases (Eisen, 1946), and widespread deposits may rarely lead to progressive muscular weakness (Weber *et al.*, 1937). Similarly, extensive involvement of *smooth muscle* in the gastro-intestinal tract has led in a few cases to dysphagia, abdominal pain with constipation or diarrhœa, and even the sprue syndrome with hypocalcæmia (Findley and Adams, 1948). *Neuropathy* from involvement of peripheral nerves has also been reported (De Navasquez and Treble, 1938; Kernohan and Woltman, 1942; Strich and Wade, 1953). Enlargement of the *liver* and *spleen* from amyloid deposition is considered to be atypical in the primary form of amyloidosis. The liver was certainly enlarged in all our patients but post-mortem examination showed this always to be due to heart failure. The spleen was never palpable during life, though in one instance (Case 3) it was found at necropsy to be moderately enlarged from amyloid deposition.

The time of survival after the onset of symptoms in our cases varied between 14 months and five years, and in general the disease was observed to run a more protracted course than would be expected from the degree of cardiac disablement present. The average survival time of 32 months, happens to coincide exactly with that of the 46 cases of primary amyloidosis reviewed by Eisen (1946) in which heart failure was stated to be the usual cause of death.

In four of the present five cases the involvement of the myocardium was conspicuous and sufficient to explain cardiac failure through mechanical interference with normal heart action as in constrictive pericardial disease (Fishberg, 1940). In Case 5, however, the infiltration of the myocardium was less extensive, and it is probable that involvement of the lungs was a factor. Only one section was available but in this there was considerable amyloid in vessels and some alveolar walls. Associated with the infiltration of smaller pulmonary arteries and arterioles there was often seen a peculiar œdematous intimal thickening with great reduction in their lumina (Fig. 13). A similar thickening was also seen in a few infiltrated coronary arteries. Its nature is uncertain but the fact that it occurred in both coronary and pulmonary arteries, and only in those with amyloid in their walls, indicates that it is a reaction to the presence of amyloid and not a result of any changes in circulatory dynamics. It is therefore regarded as an unusual form of endarteritis fibrosa producing obstruction to the pulmonary circulation. It is thus necessary to remember the primary form of amyloidosis as a rare cause of pulmonary heart disease (Sappington *et al.*, 1942).

The general distribution of the amyloid infiltration in these cases has been reviewed by Lindsay (1946). The points exemplified in the present series are the extensive but variable deposition of amyloid in the walls of blood vessels in the interstitial tissue of the heart; the infiltration, apart from vessels, in the alimentary tract and a few other organs containing smooth muscle, and very occasionally in nerves and voluntary muscles. In the heart there was no tendency for any one chamber to be especially affected, but the subendocardial zone was often extensively infiltrated. There was no involvement of liver and adrenals outside vessels, but the spleen was extensively infiltrated in one instance. In two cases there was infiltration in the kidney additional to that in the medium-sized arteries (the latter being present in all five). There was thus an overlap of distribution with that in secondary amyloidosis, and we concur with Dahlin (1949) that of all criteria given for the diagnosis of primary amyloidosis the absence of pre-existing or ætiological disease is the only constant clinical and pathological finding.

Of the 71 cases reviewed by Higgins and Higgins (1950) only 14 were recognized during life; and of these the diagnosis was established in 12 by biopsy of muscle, tongue, liver, skin, ear, nasal mucosa, or lymph glands. The correct diagnosis was made only at necropsy in four of our cases, and in the fifth only on histological examination. We would suggest that the following points are useful at necropsy examinations. It is most important to remember the possibility of amyloid disease in unexplained heart failure, and to apply the iodine test even if no other indication is present. The presence of a tough texture, a dry cut surface or a dull, waxy appearance in the myocardium is helpful, as are unexplained thickenings in the endocardium or visceral pericardium.

Thickening or deformities of valves which are not typical of chronic endocarditis may also occasionally suggest the diagnosis. More rarely, induration of other organs may provide direct information as did the typical amyloid spleen in Case 3. As is common in the primary form of amyloidosis the staining in the present material was variable, but we obtained some reaction with the accepted methods in all five cases, the avidity for Congo red being more consistent than metachromasy.

Summary

Five cases of cardiac amyloidosis are described, and their clinical and pathological features discussed.

Recognition during life is difficult, but we believe the diagnosis should be considered when otherwise unexplained heart failure, especially with normal rhythm and hypotension, is accompanied by an electrocardiogram showing equivocal changes in the T wave or defects in conduction.

Cardiac amyloidosis may occasionally simulate constrictive pericardial disease.

The extensive but variable deposition of amyloid seen in tissue at necropsy is described, and overlap in distribution between the primary and secondary forms of the disease is confirmed.

Attention is drawn to a secondary endarteritis that may involve the smaller coronary or pulmonary vessels having amyloid in their walls, and rarely may cause myocardial necrosis or pulmonary heart disease.

Suggestions are made concerning the recognition of cardiac amyloidosis at necropsy.

It is a pleasure to acknowledge the very helpful advice and criticism which we have received from Dr. William Evans and Professor Dorothy Russell. We are indebted to Sir Alun Rowlands, Sir Russell Brain, Dr. William Evans, and Dr. Kenneth Perry for permission to publish accounts of the cases under their care. Our thanks are also due to Mr. William Dicks, Mr. John King, Mr. Ernest Sheppard, and Miss S. Davies for technical help.

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ACQUIRED HEART DISEASE WITH ARGENTAFFIN CARCINOMA

BY

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Argentaffin tumours are not uncommon and have been known for over half a century—Oberndorfer called them carcinoid tumours‡ in 1907. It is surprising, therefore, that the relationship between the malignant variety of tumour and acquired heart disease was not recorded until Biörck and his colleagues published their observations in 1952. This was followed by a full description by Thorson *et al.* (1954) of a syndrome characterized by cutaneous flushing, asthma, and diarrhœa and by lesions of the tricuspid and pulmonary valves in association with metastasizing argentaffin carcinoma.

Although 23 probable cases have now been reported, very few have been diagnosed in life, so that there is a lack of precise information concerning the clinical state of the heart.

The purpose of this paper is to present the findings in a case that was unusually well-documented. For the first time, clinical examination was supplemented by phonocardiographic studies and by cardiac catheterization, which enabled one of us (M. S.) to demonstrate the removal of the excess of serotonin (5-hydroxytryptamine) from venous blood by the lungs (Goble *et al.*, 1955). Surgical exploration revealed the presence of a primary tumour with hepatic metastases and necropsy examination demonstrated the lesions in the heart and other organs.

Case Report

A 33-year-old housewife, who had been well until 1953, started to experience facial flushing and blotchy red patches on the forearms shortly after meals. Some months later she developed mild breathlessness and wheezing attacks, and at the end of 1954 a systolic murmur was noticed. She attended the National Heart Hospital for Dr. Paul Wood's opinion, and was admitted under his care in May, 1955, for further investigation, with a provisional diagnosis of pulmonary stenosis.

On admission, she was thin and confessed to having lost 21 lb. (9·5 kg.) in weight in the past two years. There was some painless diarrhœa, which had developed six weeks previously; on some occasions there had been up to ten loose motions a day, without blood or mucus. Menstruation had been irregular for the past six months. It was noted that, after most meals she became flushed, and later on, wheezy: sometimes the flushing was induced by emotion. During an attack, a diffuse erythema spread over her face from the neck, and small red patches, separated by blanched areas, appeared on the forearms. About 15 to 45 minutes after a meal, she also developed typical asthmatic wheezing, with audible sibilant rhonchi and marked retraction of the sternum, which lasted for one to two hours. Occasionally she had fleeting pains in the chest and lower abdomen.

There were telangiectases over both malar regions, and a persistent " gooseflesh " appearance of the skin. There was no cyanosis, clubbing, œdema, nor ascites. The pulse was regular with a reduced volume

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‡ These tumours are more properly known as argentaffin or Kultschitzky-cell carcinomas. This is because, as Masson showed, the tumour-cells often possess the same affinity for silver stains as the Kultschitzky-cells normally scattered in the mucosa of the small intestine and elsewhere, and also because the tumours are by no means as innocent as the term carcinoid would imply (Willis, 1948).

and the blood pressure 110/90 mm. There was a small dominant *a* wave in the jugular venous pulse. The right ventricle was not palpable but a slight systolic thrill was felt in the pulmonary area. At all areas there was a loud ejection-type systolic murmur, maximal in the second and third left interspaces, where the second heart sound was single. An atrial sound was heard but no diastolic murmur. The liver was enlarged to the level of the umbilicus. It was firm and slightly tender, and several large irregular nodules could be palpated on its surface. There was a mild hypochromic anæmia.

Radiography showed no enlargement of the heart nor dilatation of the pulmonary trunk or its main branches. There was slight reduction of the peripheral arterial shadows in the lungs. Barium-meal examination by Dr. Peter Kerley showed displacement of the stomach to the left, rapid emptying of the small bowel with disturbance of the mucosal pattern, and filling of the rectum in two to three hours.

Electrocardiography (Fig. 1) showed normal P waves, a vertical heart with clockwise rotation, slight right ventricular preponderance with dominant R waves in V4R and moderately deep S waves in V6.

Phonocardiography showed an ejection-type systolic murmur beginning late after the first sound and continuing up to a single second sound. An atrial sound was recorded at the apex and at the left sternal edge.

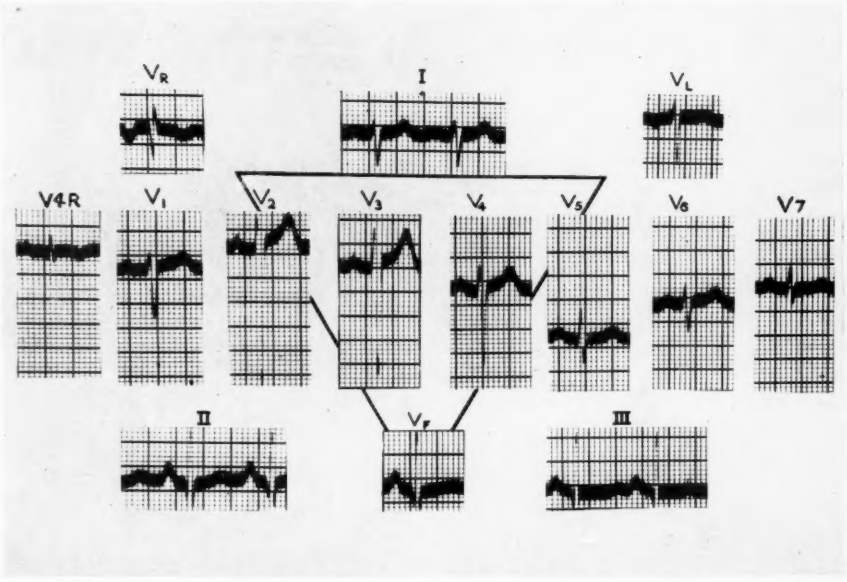

FIG. 1.—Electrocardiogram (28/6/55), showing slight right ventricular preponderance.

Cardiac catheterization was performed while the patient was fasting, and later after she had had a meal of tea and toast. This induced flushing within 15 minutes and an attack of wheezing within 45 minutes, so that observations were made at both of these times. The intrathoracic pressure-swing during the wheezing attack was recorded by an intra-œsophageal tube. The significant findings were as follows.

(*a*) Under fasting conditions, the pulmonary artery pressure on expiration was 9/4 mm. Hg, and the right ventricular pressure 56/–3 mm., indicating a pressure-gradient of 47 mm. across the pulmonary valve.

(*b*) There was no evidence of an intracardiac shunt. The blood samples from the superior vena cava, right atrium, right ventricle, and pulmonary artery had an oxygen saturation of 50–55 per cent. Those from the brachial artery were only 86 per cent saturated under fasting

conditions but the patient was asleep at this time. During the flushing and wheezing attack, however, the oxygen saturation rose to 90 per cent (the lower limit of normal for this laboratory).

(*c*) The cardiac output while fasting was 3·5 litres a minute, rising to 4·8 during flushing and falling to 3·1 litres a minute during the wheezing attack.

(*d*) The pulmonary vascular resistance remained normal throughout, being 69 dynes sec. cm.$^{-5}$ (0·9 unit) while fasting, 50 (0·6 unit) during flushing, and 78 (1·0 unit) while wheezing.

(*e*) The intrathoracic respiratory pressure-swing rose from 9 mm. Hg whilst fasting to 16 mm. during flushing and to 27 mm. during the bronchospasm. These changes were reflected in the pulmonary capillary venous pressure tracing, the last figure of which, recorded while holding the breath, was 8 mm. Hg, corresponding with a respiratory pressure-swing of 25 mm. Some respiratory pressure-swing was reflected in all pulse tracings. The findings indicated that there was some bronchospasm even when the patient was free from symptoms.

(*f*) Paradoxical pulse was revealed in the change in the left brachial artery pressure from 89/64 mm. Hg on inspiration to 109/76 mm. on expiration.

(*g*) There was a small pressure gradient of 3–5 mm. Hg. across the tricuspid valve.

Biochemistry. The history and clinical findings strongly suggested the diagnosis of argentaffin carcinoma with hepatic metastases and pulmonary stenosis. Biochemical confirmation of this was obtained by the finding of a raised serum level of 5-hydroxytryptamine and by the increased output of its excretion product, 5-hydroxyindoleacetic acid in the urine (Goble *et al.*, 1955). No abnormality was found in the serum electrolytes, the tests of liver function and the Kepler test, but the urinary excretion of 17-ketosteroids was 2·4 mg. in 24 hours.

Treatment. Although ergotamine tartrate, phentolamine, and dibenylene have some action as serotonin anti-metabolites under experimental conditions, their administration produced no clinical improvement in this patient. It was considered, therefore, that removal of the primary tumour with some of the metastatic deposits might alleviate the distressing symptoms and Sir Russell Brock undertook this at the Brompton Hospital in July. A small primary tumour 1·5 cm. in diameter was located in the ileum after careful search, together with three enlarged glands in the mesentery. Sir Russell resected the tumour with a triangle of mesentery bearing the glands, and performed an end-to-end anastomosis. He also removed a large metastasis from the liver (which was studded with them), and a hardened gland from the vicinity of the portal vein.

Unfortunately, there was no improvement following operation, and on the advice of Professor D. W. Smithers it was decided to try direct irradiation of the liver metastases with radioactive gold. Eighty millicuries of colloidal ^{198}Au was infused by slow intravenous drip in August. A temporary alleviation of symptoms followed, but a severe neutropenia developed. This subsided, however, after thirty-three days.

Progress. In September, a fresh cardiac murmur was noticed at the lower left sternal border. It was a moderately loud, late diastolic murmur which increased in intensity and length during inspiration, and it was recorded phonocardiographically. There was also a marked increase in the *a* wave of the jugular venous pulse to 6 cm. above the sternal angle, and an additional diagnosis of tricuspid stenosis was therefore made. Slight sacral and ankle œdema had now appeared.

In October, 1955, the patient was readmitted to the Heart Hospital for the last time. She was now in a sad state of mental and physical deterioration, hallucinated, depressed, emotionally labile, difficult to manage, and doubly incontinent. Sedatives and chlorpromazine afforded little relief. Œdema of the forearms developed and she sank into coma. Death ensued in November, 1955, two and a half years after the onset of symptoms.

Pathological Findings

Surgical Biopsies. We are indebted to Dr. R. C. Hallam for his report on the primary tumour and on a liver metastasis removed at operation. The primary tumour (Fig. 2) was a solitary rounded nodule, 1·5 cm. in diameter projecting into the lumen of the ileum. Its cut surface was firm, fibrous, and pale yellow, and showed nodular thickening of the submucous layer, with an intact mucosa. Microscopically, the tumour was an argentaffin carcinoma, lying mainly in the

FIG. 2.—The primary tumour in the ileum. The mucosal surface is intact over the tumour (×2).

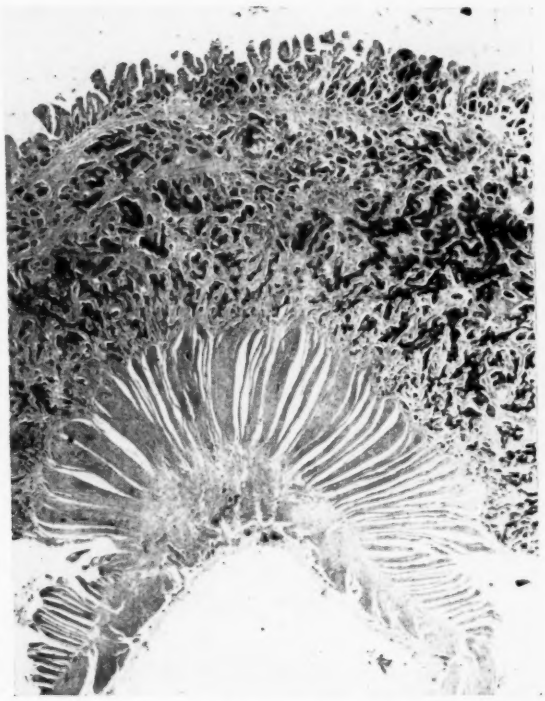

FIG. 3.—Low-power photomicrograph through the primary tumour. The dark-staining masses of tumour cells can be seen in the submucosa and mucosa (Hæmatoxylin-eosin; ×13).

submucosa (Fig. 3), although some clumps of tumour cells were found in the mucosa and traced through the muscle and serosal coats. Fontana's silver staining revealed argentophil granules in an occasional tumour cell.

Metastatic deposits were identified in the mesenteric lymph nodes and in the liver.

Necropsy examination was made by one of us (R. H.) about eight hours after death.

The subject was a woman of small physique, considerably emaciated. There was slight bronzing of the skin, most noticeable on the lower limbs, and there was a goose-flesh appearance of the skin over the shoulders. There was some œdema of the hands but none elsewhere, and there was no jaundice or cyanosis.

The *pericardium* contained about 5 ml. of clear fluid and was free of adhesions.

The *heart* was of normal size, weighing 250 g. The tricuspid valve orifice was moderately stenosed, the cusps being much thickened at their free edges and the chordæ tendineæ grossly thickened and shortened (Fig. 4). Histologically, the cusp itself showed a great increase of fibro-elastic tissue, and its borders could be followed in continuity with the elastic of the atrial and ventricular endocardium. Superimposed on both surfaces of the cusp proper were masses of rather poorly-staining fibrous tissue.

The right atrium was of normal size, with a fragment of clot adherent in the apex of the auricular appendage. The wall was a little thickened, and microscopically showed some patchy thickening of

FIG. 4.—Tricuspid valve after cutting open. The cusps are much thickened at their free margins, and the chordæ tendineæ greatly thickened and shortened. There is also slight hypertrophy of the right ventricle (about natural size).

the endocardium. The right ventricle showed early hypertrophy, measuring up to 0·5 cm. in thickness; otherwise it was normal.

The pulmonary valve was more affected than the tricuspid. The orifice was stenosed to a triangular shape, and the cusps were grossly thickened, shrunken and made rigid by tough fibrous tissue which extended down to the endocardium of the infundibulum. The sinuses of Valsalva were greatly reduced. Fig. 5 is a view of the intact valve from above comparing the pulmonary valve on the right with the aortic valve on the left. Fig. 6 shows the pulmonary valve after cutting, and illustrates how the valve site forms a constricting waist between the pulmonary trunk and the infundibulum of the right ventricle. Microscopically, the appearances were similar to those of the tricuspid valve. The cusp proper showed extensive fibroelastosis, the elastic being in continuity with that in the pulmonary trunk. The borders of the cusp were sharply demarcated from the masses of fairly acellular fibrous tissue covering both surfaces of the cusp (Fig. 7). There were some areas of more active fibrosis, and a few lymphocytes in places.

The left atrium was of normal size, but showed some thickening of the endocardium due to fibroelastosis, which was associated with some degeneration of the plain muscle. The myocardium showed an increase of interstitial tissue. The left ventricle was up to 1·3 cm. thick, but not dilated. Microscopically, there was some increase of interstitial tissue with one or two areas of more extensive replacement fibrosis, and the epicardium showed a few scattered round cells, as it did in the other heart sections.

The mitral valve appeared normal, but histological examination revealed what appeared to be a fairly recent thrombotic lesion on one of the cusps. The aortic valve was normal apart from a little thickening in the extreme bases of the cusps: this can be seen in the top, left cusp of Fig. 5.

The foramen ovale was sealed and the ductus arteriosus closed. The coronary arteries were virtually free from atheroma (although the left circumflex artery was smaller than usual). There was minimal atheroma in the aorta and in the pulmonary arteries, and the great veins were normal.

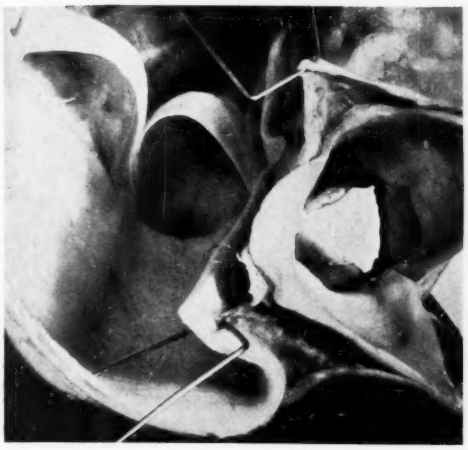

FIG. 5.—Intact pulmonary valve viewed from above to show the greatly thickened cusps, the small sinuses of Valsalva, and the stenosed triangular orifice. On the left are two aortic cusps for comparison. There is some thickening visible in the base of the upper aortic cusp (about natural size).

FIG. 6.—Pulmonary valve after cutting open. The cusps are shrunken and greatly thickened by tough fibrous tissue which is spreading down into the infundibulum of the right ventricle. Note how the valve site forms a constricting waist between the pulmonary trunk and the infundibulum (about natural size).

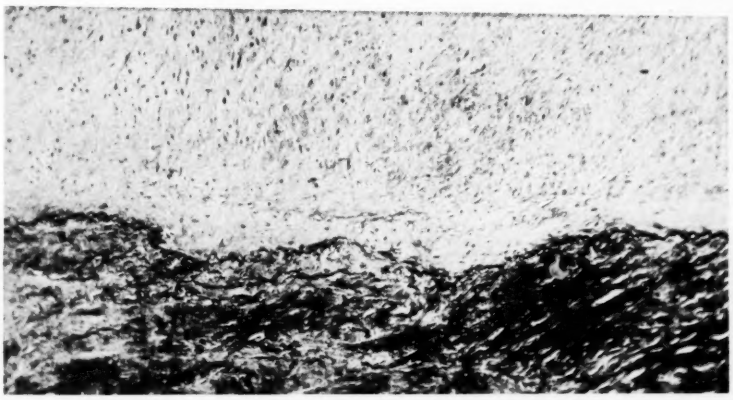

FIG. 7.—Pulmonary valve cusp. The cusp proper shows much fibroelastosis (at bottom of picture). Superimposed on it is a mass of fibrous tissue. Note the sharp boundary (Elastic van Gieson; ×92).

The *peritoneum* showed numerous strong adhesions at the operation site, but no free fluid. The liver was enlarged to 2200 g. and was partly adherent to the anterior abdominal wall. Its surface was studded with scattered, neatly-rounded, raised, creamy-white metastases, and on slicing, these were seen to be concentrated in the right lobe (Fig. 8) to form a mass measuring 7 × 12 cm., partly necrotic in the centre. Elsewhere, the liver parenchyma was pale. Microscopically, the tumour showed the structure of an argentaffinoma, the tumour cells being in neat, well-defined masses, with numerous blood sinuses in direct

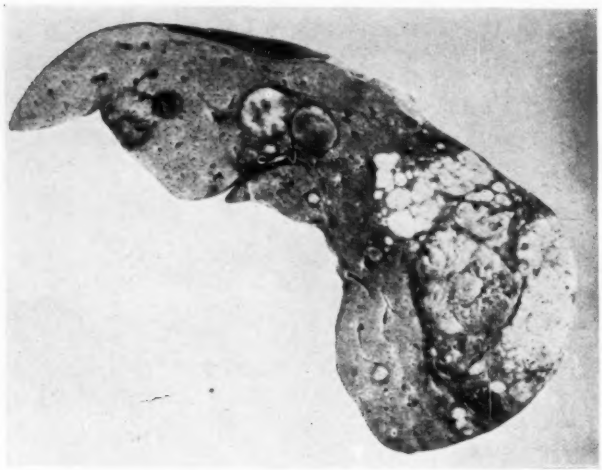

FIG. 8.—Slice of liver, showing the argentaffin carcinoma metastases concentrated in the right lobe (about $\times \frac{1}{2}$).

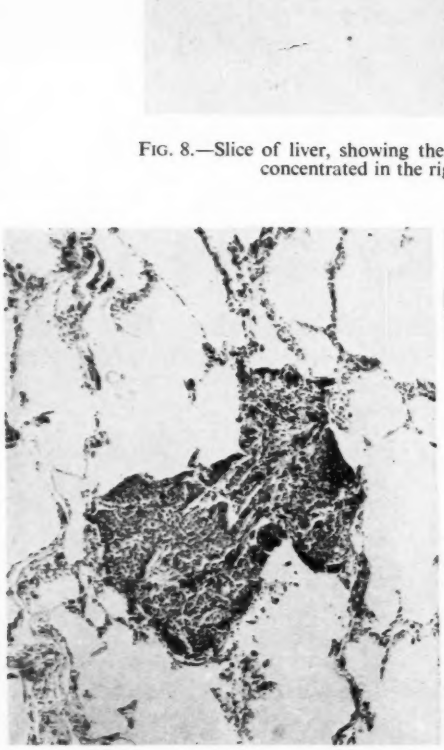

FIG. 9.—Lung metastasis (Hæmatoxylin-eosin; ×76).

FIG. 10.—Lung. Group of tumour cells in a capillary in centre of picture (Hæmatoxylin-eosin; ×290).

contact with tumour cells. There was some attempt at fibrous encapsulation of the metastases. The argentophil reaction (Masson–Fontana) was negative.

The *lungs* showed moderate congestion only and appeared well aerated, but on histological examination numerous microscopic metastases were seen in all areas. The largest one seen is illustrated in Fig. 9 while Fig. 10 shows a group of tumour cells, possibly an embolus, in a lung capillary. There were also

widespread bronchitis, and patches of early bronchopneumonia in all areas, with a little emphysema. The vessels showed no lesion.

Other Viscera. There was no tumour in the abdomen apart from the liver metastases. The ileal anastomosis, situated about 50 cm. from the ileo-cæcal valve, was perfectly healed. Silver methods failed to reveal any excess of argentophil cells at the site of the operation, or in sections from other parts of the intestine. The *spleen* weighed only 80 g. but showed no lesion. The *kidneys* showed congestion only, each weighing 120 g. The *brain* weighed 1400 g. and showed no lesion. The *lymph-nodes* were inconspicuous: sections of abdominal and thoracic nodes revealed no metastases microscopically.

Discussion

The physiological studies showed only a moderate degree of pulmonary stenosis, which is in agreement with the slight degree of right ventricular hypertrophy demonstrated cardiographically and at necropsy. In several of the cases described by Thorson *et al.* (1954), however, there was moderate right ventricular hypertrophy at necropsy although there was only slight pulmonary stenosis. Signs of tricuspid stenosis developed while the patient was under observation, although cardiac catheterization had earlier demonstrated a small diastolic pressure gradient across the tricuspid valve. The finding of normal pulmonary vascular resistance during flushing, when circulating serotonin was increased, refutes the suggestion by Thorson *et al.* (1954) and Jenkins and Butcher (1955) that the pulmonary stenosis is in some way the result of increased pulmonary vascular resistance due to vasoconstriction of pulmonary arterioles by serotonin.

The necropsy findings in this case agree with those in the 18 already reported: in 15 of these there was pulmonary stenosis, in 10 some tricuspid abnormality, and in 4 minor changes, such as we have described, in the mitral and aortic valves (Rosenbaum *et al.*, 1955; Jenkins and Butcher, 1955; Bean *et al.*, 1955). The patchy thickening that we found in the endocardium of the right atrium was reported in three cases (Thorson *et al.*, 1954; Branwood and Bain, 1954). The gross changes in the tricuspid and pulmonary valves correspond in general with the description of others —sclerotic thickening of the cusps, often with fusion of the commissures. In our case, there was almost no inflammatory reaction, though Biörck *et al.* (1952) reported round cell infiltration in one case.

There is increasing evidence (Pernow and Waldenström, 1954; Page *et al.*, 1955; Sjoedsma and Udenfriend, 1955) that the various features of the syndrome are related to the presence of large amounts of circulating serotonin, which is secreted by the primary tumour and its metastases. This was clearly demonstrated in our case (Goble *et al.*, 1955). Similar mental changes to those in our case were observed once by Jenkins and Butcher (1955). It is believed by Woolley and Shaw (1954) that certain psychoses, such as schizophrenia, may be related to disturbed serotonin metabolism.

The pathogenesis of the cardiac lesions remains obscure. It was shown (Goble *et al.*, 1955) that the serotonin content of pulmonary artery blood was higher than that of blood in the brachial artery or superior vena cava. It was suggested that this was due to removal of serotonin by the enzyme mono-amine oxidase, which is known to be present in lung tissue in high concentration and to have the property of inactivating serotonin (Bradley *et al.*, 1950). The high concentration of serotonin in right-heart blood may alter the endothelium, by increasing cellular permeability (Pickles, 1955) and allowing platelet deposition on the valve cusps, with subsequent fibrosis. In this connection, the minor changes found in the aortic and mitral valves in our case are of interest in view of the presence of lung metastases.

Summary

A case is reported of argentaffin carcinoma of the ileum with hepatic metastases, pulmonary and tricuspid stenosis, flushing, asthma, and diarrhœa.

Cardiac catheterization studies, reported for the first time in this condition, confirmed the presence of pulmonary stenosis, indicated a slight degree of tricuspid stenosis, and showed normal

pulmonary vascular resistance during fasting, flushing, and wheezing. It also permitted original observations on serotonin metabolism which throw some light on the pathogenesis of the syndrome.

Removal of the primary tumour did not relieve symptoms, but temporary improvement followed the administration of radio-active colloidal gold.

The pathological findings in our case are described and the pathogenesis of the syndrome discussed.

We wish to thank Dr. Paul Wood, under whose care the patient was admitted, for permission to publish this case and for his valuable criticism. We are indebted to Sir Russell Brock for the findings at operation, to Dr. R. C. Hallam for his report on the surgical material, and to Mr. D. F. Kemp for Fig. 2 and 3. Finally, we express our gratitude to Professor R. A. Webb for his interest and kindness in providing laboratory facilities, and to Dr. D. N. Baron and Dr. J. C. Leonard for their constructive criticism.

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CASE REPORTS

TRUNCUS ARTERIOSUS AND A SINGLE VENTRICLE

BY

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A truncus arteriosus in association with a single ventricle is very rare and Siddoway and Chernish (1952) found only 16 possible recorded cases. In few instances has the clinical picture been described, and in all the cause of death has remained obscure.

Case Report

R. S., a full-term male infant weighing 5 lb. 9 oz. was born in the Obstetric Department of the Mayday Hospital following a surgical induction of labour at $39\frac{1}{2}$ weeks for a very mild pre-eclamptic toxæmia (B.P. 150/90 and a trace of albuminuria). Pregnancy and delivery were otherwise normal and the fœtal heart sounds were regular during labour. The baby was covered in meconium but was otherwise normal and cried well. The placenta was small and infarcted.

The baby remained well and took its feeds normally until 42 hours after birth when cyanosis developed and there was dyspnœa on handling and feeding. There was a loud systolic murmur over the præcordium maximal in the pulmonary area but no thrill was palpable. The lungs were clear. A diagnosis of congenital heart disease—probably tetralogy of Fallot—was made.

On the fourth day after delivery, tube feeding was commenced and continuous oxygen was given into a tented cot. Dyspnœa and cyanosis became worse and it was thought that broncho-pneumonia was developing. Penicillin was given and an "alevair" aerosol was passed into the tent. Pitting œdema, periodic gasping respiration, and lowered body temperature developed and coarse râles were heard all over the chest with impaired percussion note at the lung bases. By the morning of the fifth day considerable improvement with disappearance of the œdema had occurred. However, a sudden attack of intermittent gasping respiration and deep cyanosis occurred, frequent loose motions were passed, and ten minutes later the child died.

Necropsy. Full-term male infant with cyanosed head and extremities. On opening the chest, intense pulmonary congestion was seen, but the heart was not enlarged, the transverse diameter being 3·8 cm. (Fig. 1). The right atrium was moderately enlarged, the left being rudimentary and receiving blood from the pulmonary veins but having no connection with the ventricle. A patent foramen ovale 2 mm. in diameter had a crescentic valvular fold at its lower margin. The tricuspid valve was normal and there was no evidence of a septum in the single ventricle (Fig. 2). A single arterial trunk 1 cm. in diameter gave off the pulmonary arteries, each 3 mm. in diameter, and continued as the aorta, giving off innominate, left carotid, and left subclavian branches. A three-cusp valve guarded its base but no coronary ostia were found.

A single coronary artery 2 mm. in diameter arose from the innominate artery and passed down behind the large trunk between it and its pericardial sheath to the base of the heart where it divided into a right coronary artery running down the atrioventricular groove to supply branches to the right atrium and anterior surface of the ventricle, and a left marginal artery running down the left margin of the ventricle to the apex and supplying branches to the posterior surface of the ventricle. On sectioning the ventricular wall no rudimentary chamber was found. The descending aorta was of normal size. There were no other abnormal findings.

This case thus follows exactly the pattern of a truncus arteriosus of the solitary pulmonary trunk type. Its interest lies in the presence of ante-mortem general œdema and post-mortem pulmonary congestion.

Family History. The mother was operated on as a baby for pyloric stenosis. She had had rubella, mumps, measles, chickenpox, scarlet fever and severe rickets as a child. She could remember no mild illness during the pregnancy, which was her fifth.

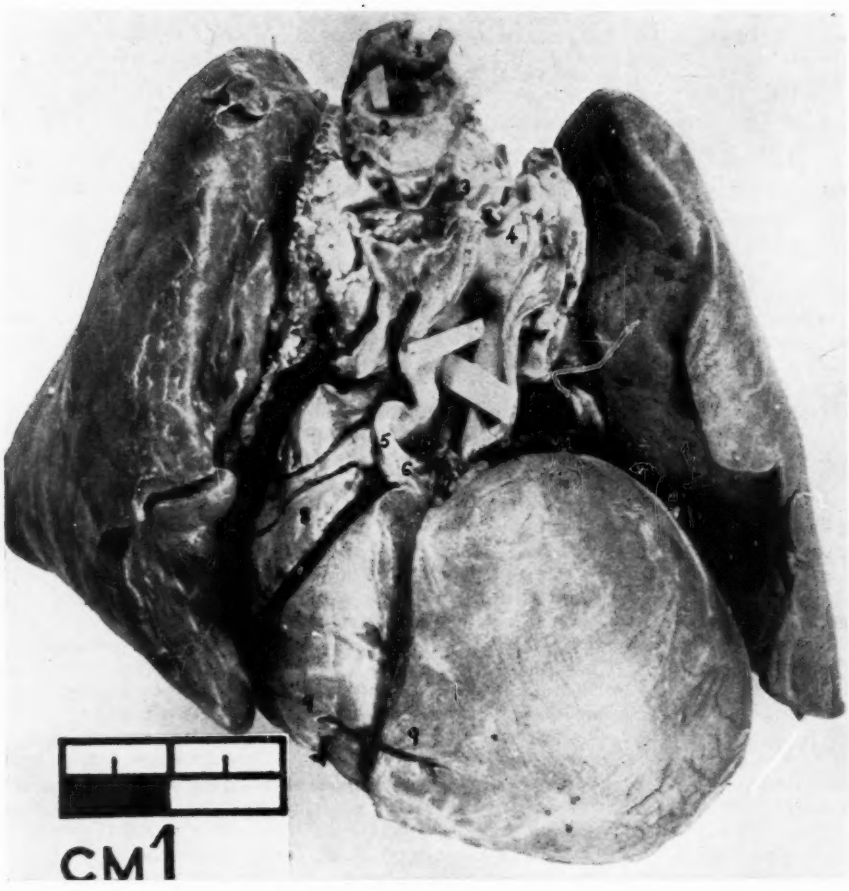

FIG. 1.—Heart from 5-day-old baby, showing a single trunk leaving the common ventricle. This trunk has been opened to show the orifices of the pulmonary arteries which are illustrated by white markers. (1) œsophagus; (2) trachea; (3) innominate artery; (4) transverse aorta; (5), (6), (7) valve cusps; (8) right atrium; (9) common ventricle.

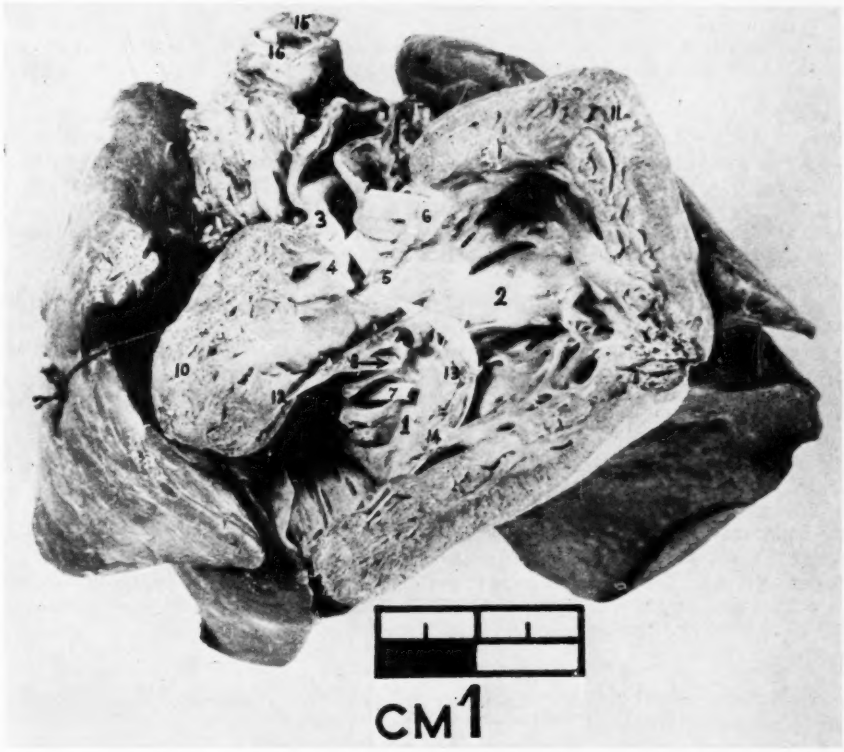

FIG. 2.—The heart has been opened to show the large right atrium, the common ventricle and the truncus arteriosus with a three-cusped valve at its base leaving the ventricle. (1) Right atrium; (2) common ventricle; (3) truncus arteriosus; (4), (5), (6) valve cusps illustrated by markers; (7) marker in patent foramen ovale; (8) marker showing entry of superior vena cava; (9) transverse aorta (continuation of truncus arteriosus; (10), (11) reflected flaps of ventricular wall; (12), (13), (14) cusps of tricuspid valve; (15) œsophagus; (16) trachea.

Her first pregnancy ended in a stillbirth at 33 weeks with breech extraction of a male fœtus having deformed feet and genitalia. Her second pregnancy and delivery were normal but the boy was operated on at three weeks for pyloric stenosis. The third pregnancy and delivery were normal. The fourth pregnancy yielded a stillbirth at 40 weeks. The mother had a sister who had three miscarriages (one at six months) and two normal children. There was no other relevant family history.

Discussion

Three different developmental varieties of a single arterial trunk with a single ventricle all having a common clinical picture have been described.

(1) True truncus arteriosus communis persistens in which one abnormally large vessel leaves the heart giving rise to both systemic and pulmonary circulations without evidence of a second atretic vessel. The coronary arteries arise from its base.

(2) Solitary aortic trunk in which the pulmonary blood supply comes from the ductus arteriosus or from a collateral bronchial vessel and in which there may be evidence of an atretic pulmonary artery.

(3) Solitary pulmonary trunk in which an atretic aorta may be obvious or represented by a single coronary vessel given off from the main vessel or one of its major branches as in the above case.

The history of the present case and the findings on necropsy are typical, few cases surviving more than 20 days.

The case reported by Mehta and Hewlett (1945) was unique in surviving 56 years before death occurred from congestive cardiac failure in association with chronic bronchitis and unique in having a functioning mitral valve.

The most serious defect would thus appear to be the absence of a satisfactory return of blood from the lungs through a functioning mitral valve and it is probable that the cause of death, which is so poorly understood, is pulmonary œdema as a result of obstruction to the return of blood from the lungs—in effect a functional mitral stenosis of extreme degree. The obstruction might result at the foramen ovale from gradual closure of the orifice or from increased pressure in the right atrium due to a mild functional tricuspid incompetence. The increased systemic load produced by the effort of feeding or by anoxia could produce such incompetence by dilatation of the ventricle, thus precipitating a vicious circle which would inevitably end by death.

The only other explanation as to the cause of death is that offered by Rodgers and Edwards (1951), namely that an intra-pulmonary pulmonary stenosis occurs resulting from the single ventricle ejectile force which sends blood to both the pulmonary and systemic circulations. This explanation seems unlikely in view of the pronounced pulmonary congestion found at autopsy in all cases. Furthermore, it does not explain the long survival in the case of Mehta and Hewlett which is unique in the existence of a functioning mitral valve, because the pulmonary arteries must have been subjected to the same single ventricle ejectile force.

In the case now described the presence of ante-mortem œdema suggests a rise in pressure on the right side of the heart which would inevitably block the left-to-right shunt through the patent foramen ovale and thus lead to total obstruction of the pulmonary circulation, pulmonary congestion, and death.

The presence of other congenital abnormalities in the relatives of the case under discussion and the high fœtal mortality in this family suggests some fundamental disorder that is affecting the embryos at an early stage of development. The coincident appearance of other abnormalities in the same child in several reported cases would suggest that if the disorder is a genetic one rather than an environmental one it is not related to a specific organ.

Summary

The clinical picture and post-mortem findings in truncus arteriosus associated with a single ventricle are discussed with illustration of a case.

The interesting hæmodynamics of these cases are considered and a rise of pressure in the right atrium consequent upon dilatation of the common ventricle to cope with an increased systemic load is postulated as a cause of arrest of the pulmonary circulation and death.

I wish to thank Dr. C. O'Connor of the Mayday Hospital, Croydon for the pathological specimen, Dr. J. Bevan-Jones, Mr. A. F. Clift, and Dr. N. Jackson of the Mayday Hospital, Croydon for the clinical notes and for permission to publish, and Mr. A. Blyth of University College Hospital for the photographs.

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THE EFFECT OF DIGITALIS ON NODAL RHYTHM WITH RECIPROCAL BEATS

BY

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From the Belfast City Hospital

When the A-V node is the dominant pace-maker of the heart, the effect of drugs on its fundamental properties can be studied, especially with reference to the duration of its refractory period and the rate of anterograde and retrograde conduction. Digitalis has been observed to precipitate reciprocal rhythm (White, 1915; Blumgart and Gargill, 1930, Case 1). Dechard and Ruskin (1943) related the concentration of digitalis in the body to the effect produced on the A-V node. They found that digitalis delays conduction in the A-V node, retrograde conduction proportionately more so than anterograde conduction, the effect increasing with the accumulation of the drug in the body, although in the initial stages of digitalization retrograde conduction was accelerated. Their recovery curves for anterograde conduction, obtained by graphically relating the R–P and P–R intervals, showed an apparent delay of recovery of the A-V node, being most conspicuous when retrograde conduction was much prolonged.

Details of Observations

A man, aged 45 years, weighing 8 stone (59 kg.), was known to have a dominant nodal rhythm with recurrent spontaneous reciprocal beats. Full details of an experimental study of this case have already been reported (Fletcher and Stevenson, 1955). He remained resting in bed throughout the period of observation, and received no drugs likely to influence the mechanism of the heart beat, other than the experimental dose of digitalis. A control cardiogram was taken immediately before administration of 0·5 mg. digoxin (B. W. & Co.), by mouth on a fasting stomach. No gastric upset occurred, although previous experience had revealed extreme sensitivity even to small doses of digitalis. Serial cardiograms were recorded at one, three, and six hours after the administration of the drug. Long strips of lead II were used to study the changes in the heart beat. Analysis of these records confirmed that the digitalis had a significant effect on the cardiac rhythm which was essentially similar in all the tracings. After twenty-four hours, the cardiogram resembled the control record. Representative cuttings from the control cardiogram and the cardiogram at the end of the third hour are shown in Fig. 1 and 2 respectively. Table I records the measurements of the conduction times in the electrocardiogram of Fig. 1, and Table II those of Fig. 2.

TABLE I

CONDUCTION TIMES OF HEART BEATS IN ELECTROCARDIOGRAM OF FIG. 1

Beat No.	1	2	3	4	5	6	7	8	9	10
R–P in $\frac{1}{100}$ sec. . .	11	28	10	28	12	31	13	30	9	22
P–R in $\frac{1}{100}$ sec. reciprocal beats	—	39	—	37	—	30	—	28	—	35

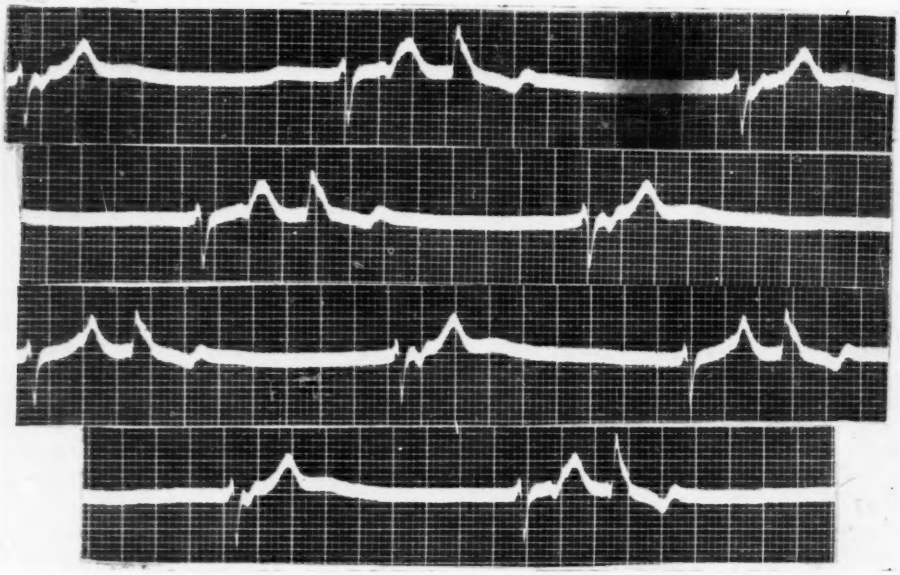

FIG. 1.—Control. Alternating reciprocal beats. Time marker 0·04 and 0·2 sec. Continuous strip lead II.

Fig. 1 demonstrates a dominant nodal rhythm with spontaneous alternating reciprocal beats, so often found in experimental tracings (Scherf—personal communication). The reciprocal beats are manifest after the longer R–P intervals (Table I). It is difficult to explain the reason for the common alternation of the R–P intervals. The rule of a fatigue and recovery mechanism may play a role by altering the time sequence of atrial and ventricular activation of post-extrasystolic beats, when nodal rhythm with pre-ventricular activation is complicated by ventricular ectopic beats without retrograde conduction (Scherf and Shookhoff, 1925).

The Effect of Digitalis

Fig. 2 reveals an increased incidence of ectopic beats. There appears to be no doubt that the ectopic beats following nodal beats No. 7, 8, 9, and 10 are due to a return mechanism. The R–P intervals in Table II are significantly prolonged compared with the control record (Table I). In fact the R–P intervals following beats No. 1, 4, and 5 in Table II are most unusually prolonged, and the beats that immediately follow them closely resemble the beats of the dominant rhythms, whereas the other ectopic beats in Fig. 2 show varying degrees of ventricular aberration which is commonly associated with reciprocal beats. Caution is necessary not to confuse A-V nodal beats

TABLE II

CONDUCTION TIMES OF HEART BEATS IN ELECTROCARDIOGRAM OF FIG. 2

Beat No.	1	2	3	4	5	6	7	8	9	10
R–P in $\frac{1}{100}$ sec. . .	59	—	28	73	68	—	24	44	33	22
P–R in $\frac{1}{100}$ sec. reciprocal beats	16	—	34	16	20	—	40	16	28	39

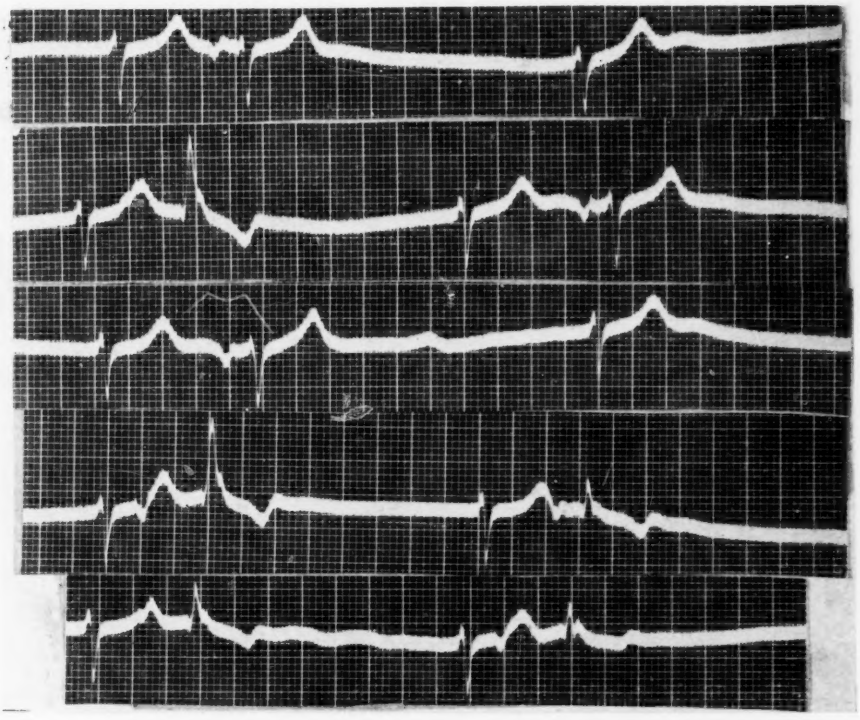

FIG. 2.—Effects of digitalis. Time marker 0·04 and 0·2 sec. Continuous strip lead II.

and escaped beats with reciprocal rhythm. However, measurements of the auricular cycle lengths of Fig. 2 prove that there is a disturbance of the auricular rhythm—the fourth auricular cycle length measures 0·286 sec. and the ninth 0·204 sec. The disturbance of auricular rhythm combined with negative P waves " jammed " between two ventricular complexes supports the diagnosis of reciprocal rhythm and the ectopic beats following nodal beats No. 1, 4, and 5 in Fig. 2 may well be due to a re-entry mechanism. The P–R intervals in Table II are generally shorter than in Table I, and in case of beats No. 1, 4, 5, and 8, Table II, they are within the normal range. The shortening of the period of anterograde conduction is a direct consequence of the lengthening of the period of retrograde conduction, which permits more complete recovery of the A-V node from its state of relative refractoriness following nodal discharge.

Discussion

There is no doubt that reciprocal beats in nodal rhythm are due to a re-entry mechanism (Scherf, 1941; Dechard and Ruskin, 1943). Retrograde conduction through the A-V node must be delayed to a certain critical level just greater than the absolute refractory period of the nodal tissues for a reciprocal beat to become manifest. In this case digitalis delayed retrograde conduction, so increasing the incidence of reciprocal beats. There is no evidence that digitalis had any effect on the absolute refractory period of the A-V node. Thus in beat 10 of both Fig. 1 and 2, a reciprocal beat is manifest after an R–P interval of 0·22 sec., i.e. a fraction greater than the critical value (0·2 sec.) for reciprocation to occur in this case (Fletcher and Stevenson, 1955).

Summary

The effect of an experimental dose of digitalis on nodal rhythm with reciprocal beats is analysed. Digitalis significantly delayed retrograde conduction through the nodal tissues, resulting in an increase in the incidence of reciprocal beats. Anterograde A-V conduction and the absolute refractory periods of the A-V node were not influenced by digitalis under the conditions of observation.

We wish to acknowledge the helpful advice of Dr. David Scherf, New York Medical College.

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BICUSPID PULMONARY VALVE IN ASSOCIATION WITH CALCIFIC AORTIC STENOSIS

BY

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The ætiology of aortic stenosis in the presence of a normal mitral valve is obscure, the major possibilities being old rheumatic infection and calcification of a congenitally abnormal valve. The present report describing a healthy pulmonary valve with only two cusps occurring in association with a typical extreme calcific aortic stenosis, therefore, throws some light on this subject.

Case Report. A married woman of 56 had a history of 5 years of increasing breathlessness. Eighteen months before she died she had a pain in the calf and chest, and a year later swelling of the ankles first appeared. She next developed pains in the abdomen and in the chest and then had transient congestive cardiac failure. Two weeks before death there was more chest pain and retention of urine; this contained protein and urobilinogen. The blood urea rose to 153 mg. per 100 ml. while the serum sodium and chloride fell to 290 mg. and 455 mg. respectively. Her E.S.R. was 21 mm. in the first hour (Wintrobe). She died in uræmic coma.

Necropsy. There was slight icterus and some dependent œdema. The heart weighed 575 g. and was covered with a fibrinous exudate from a small effusion. This cardiomegaly was due to hypertrophy of the left ventricle (average thickness 28 mm.) and some dilatation of the right ventricle (5 mm.) and atrium. The tricuspid and mitral valves were somewhat opaque; the chordæ of the former were normal while those of the latter showed some thickening and shortening but no matting or grouping to suggest rheumatism. Both orifices were normal. The most significant abnormality was that the pulmonary valve had only two cusps, the posterior one being slightly larger and bearing at its mid point a transverse ridge-like elevation. They were quite transparent and there was no fibrosis. The circumference was 75 mm. at the level of the commissures. The aortic valve was grossly diseased being irregularly calcified and ulcerated so that it formed a dome-shaped protrusion into the aorta. Its slit-like orifice was nearly antero-posterior and measured 19 × 7 mm.; the front end abutted the nodule on the posterior pulmonary cusp. It seemed originally to have been bicuspid, too, its right-hand cusp bearing a nodule similar to that on the pulmonary valve. The right coronary artery arose from two orifices 2 mm. apart in the anterior part of the right sinus in front of the nodule. There was a small mural thrombus in the right atrium.

There were multiple organizing pulmonary infarcts with effusions and evidence of chronic passive congestion in the other organs. Organizing thrombi of considerable age were present in the œdematous calf of the right leg. There were no histological abnormalities in the myocardium, nor, apart from congestion and infarction, in the lungs. No organic cause for the uræmia was found.

Discussion

Aortic valves apparently composed of only two cusps are relatively common and though they are generally found to be stenosed there is little direct evidence of the cause of this distortion. Neither rheumatic infiltrations diagnosed histologically (Karsner and Koletsky, 1947) nor a clinical history reaching back into childhood (Campbell and Kauntze, 1953) are more than suggestive. Bicuspid malformation of the pulmonary valve, on the other hand, is extremely uncommon and a healthy bicuspid valve in a heart that does not have some fairly gross abnormality of septa or origin of great vessels may well be unique. Most examples occur in some form of the tetralogy of Fallot, 7 of the first 18 cases in the Guy's Hospital series of necropsies showing this abnormality: one of these had also aortic stenosis (Campbell and Brinton, 1953). In isolated pulmonary valvular stenosis apparent bicuspid malformation of the contracted pulmonary valve is much less common, none of 14 consecutive cases showing it, but one of these had a bicuspid aortic valve (Campbell, 1954).

Since a bicuspid pulmonary valve is usually associated with some other error of cardiac

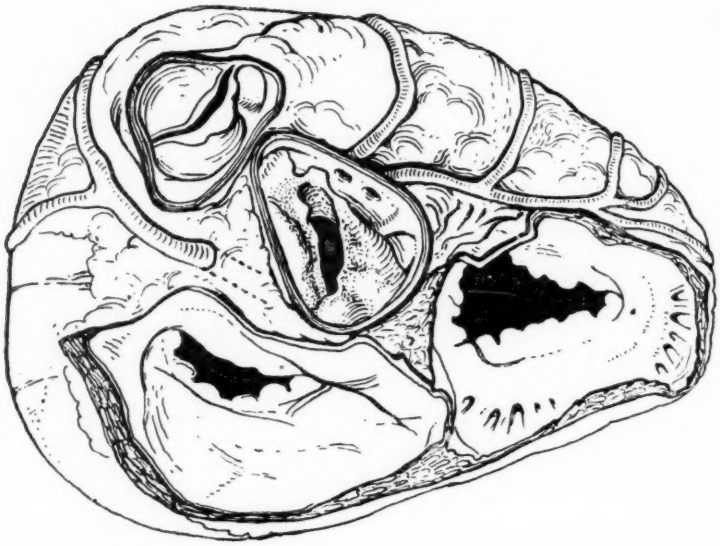

FIG. 1.—View of the base of the heart after dissection of coronary arteries and removal of atria and supravalvular parts of aorta and pulmonary artery. The pulmonary valve was normal except for the fact that it was composed of two cusps. The aortic valve was grossly distorted and calcified and seemed originally to have been bicuspid also.

development the associated abnormality in this heart was probably congenital in origin. This was, however, typical of the sort of aortic malformation that would, if present alone, commonly be considered to have developed after birth. This heart is described as a piece of evidence supporting the suggestion that many of these lesions, although first responsible for symptoms late in life, are in fact congenital in origin.

Summary

A case of congenital biscuspid malformation of a normal pulmonary valve in the absence of any other abnormality of the septa or orientation of the great vessels but associated with gross calcific aortic stenosis is described. The aortic malformation is apparently superimposed on a bicuspid form of that valve and it is suggested that the present case is evidence that some of these distorted aortic valves are congenital in origin rather than acquired.

I wish to thank Dr. Hampson, Physician to Guy's Hospital, under whom this patient was admitted, for permission to publish this report.

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ALFRED HOPE GOSSE

Alfred Hope Gosse, the son of a doctor, was born at Wallaroo in South Australia in 1882. After attending St. Peter's College, Adelaide, he came to England and entered Gonville and Caius College, Cambridge, where he graduated in 1907. He completed his medical course at St. Mary's Hospital, winning the Cheadle gold medal for clinical medicine, and qualified in 1910. He was successively house physician, medical officer in the inoculation department, and medical registrar at St. Mary's, before he became research assistant to Sir James Mackenzie at the London Hospital in 1914. In that year also he was elected to the staff of the Brompton Hospital.

When war broke out he served as registrar at the Third L.G.H. (Territorial) and in 1916 volunteered for service in Mesopotamia where at first he was stationed with the 40 B.G.H. at Basra. His administrative skill caused him to be chosen as commanding officer for the Officers' Hospital, a large Arab mansion at Beit Naama on the banks of the Tigris, where he did excellent work.

On his return to England in 1919, Hope Gosse was appointed physician to outpatients at St. Mary's Hospital, where he specialized in diseases of the heart and lungs, while retaining an interest in all branches of medicine. He had a large private practice but never let this interfere in the slightest with his hospital duties which he carried out most faithfully. He was a wise and enthusiastic teacher and a good friend to the students. During the war of 1939–45 while serving in the E.M.S. he spent a large part of his time at St. Mary's, living and mingling with the students and doing a great amount of teaching. He retired from hospital eight years ago but continued private practice for a few years longer.

From 1942 he was the independent medical expert in diseases of the chest and heart to the Ministry of Pensions, where his clearly expressed and carefully reasoned opinions were highly valued. He served on the committee to consider whether amputation of a limb and the wearing of a prosthesis could in the course of time initiate or aggravate cardiovascular disorders. For more than twenty years he was medical officer to the Medical Sickness Insurance Society and took great interest in this work. His common sense and good judgement must have played an important part in building up the success of the Society. From the information he obtained in this way he wrote *The Health of the Doctor* dealing with the morbidity and mortality from various diseases (*Brit. med. J.*, 1942, **2**, 567). He did not agree that coronary disease was specially common in doctors and thought its high incidence in the Registrar-General's returns was largely due to more accurate diagnosis in doctors.

He was a painstaking rather than a ready writer of medical articles; he wrote and rewrote them and would alter them again and again to get the exact sense that he wished. At one time he had been editor of St. Mary's Hospital Medical School Gazette and this had made him a judge of good writing. He wrote on *The Heart and its Rhythm in Acute Rheumatism* with Gunson and Parkinson (*Quart. J. Med.*, 1920, **13**, 363) and on *The Heart in Pulmonary Tuberculosis* with Wingfield (*Brit. J. Tuberc.*, 1937, **31**, 92) and more recently with Oram the section on *Embolism* in the *British Encyclopaedia of Medical Practice*.

After retirement he gave time to interests that he had at heart. He was chairman of the distribution committee of the Hospital Sunday Fund, and interviewed many hospital almoners and took immense trouble to see that the grants should be given to objects for which the National Health Service made little or no provision.

Hope Gosse was tall and broad in proportion, and fresh-coloured. He walked with a very slight stoop at the shoulders. His face had a pleasant placid expression, sometimes a little quizzical. He shrank from public speaking but loved a private discussion. He was very fair-minded and always

ready to listen to the other side of the question: he took long to make up his mind, but after going over every argument carefully and reaching a decision, he seldom changed it. Thus as adviser to the Ministry of Pensions he had considered very carefully whether cardiac infarction was in any way due to service conditions, and having made up his mind that the evidence was against this he was reluctant to make exceptions.

He was conscientious to a fault and almost over-scrupulous. In financial matters he was accurate and punctilious: his first care was to lay aside from his income that which would be needed for the income tax, which he always paid as soon as he received the demand note. As treasurer of the Medical Society of London he greatly improved its financial position; one particular investment he watched for twenty years until it reached a value that he had hoped for, when he sold with great advantage to the society. He had great self-control; for many years he was a heavy cigarette smoker, but came to the conclusion that he was becoming a slave to the habit and gave it up at once and for ever.

His word was his bond and there were few who could equal his reliability. He was a faithful friend and many are the men whom he helped in their hour of need. All his actions were above board and the slightest suspicion of any underhand action in others excited his disgust. Hope Gosse was modest and retiring but he was very sociable and popular. He was at different times president of the Harveian Society and the Medical Society of London. At one time he was a very good bridge player, and he loved to watch a cricket match. Though Australian born he was an impartial onlooker, and when asked which side he favoured gave the characteristic reply—" the side which is doing badly." He also enjoyed a good race-meeting at Goodwood or Ascot.

He never married and for a long time his mother lived with him in his attractive Harley Street home, surrounded by good furniture and pictures, in which he was interested. He was always fond of children and they of him and for years would not miss the Christmas festivities at his hospital where he played the part of Father Christmas to their great delight.

As a cardiologist, Hope Gosse early recognized the significance of the symptoms of his fatal disease, and characteristically put all his affairs in perfect order before going into hospital. He never liked to cause anyone trouble and almost his last words were those of apology to the nurses for any trouble he was causing them. By his departure his many friends have lost an influence in their lives that they can never hope to regain.

ZACHARY COPE
JOHN PARKINSON

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

The THIRTY-FIFTH ANNUAL GENERAL MEETING of the British Cardiac Society was held at Manson House, London, on Thursday, May 24, 1956. The Chairman, EVAN BEDFORD, took the Chair at 9.30 a.m.; 148 members and 15 visitors were present.

PRIVATE BUSINESS

1. The minutes of the last Annual General Meeting, having been published in the Journal (**17**, 573, 1955), were taken as read and confirmed.
2. The Chairman thanked Sir John Parkinson for his help and guidance during his four years' office as President, and announced that Maurice Campbell, having been duly elected, was now taking over the duties of President.
3. The Chairman thanked Sam Oram for his work as Secretary during the last five years, and Patrick Mounsey, who had been appointed Secretary, took office.
4. The Balance Sheet for 1955–56 was presented, having been audited and found correct by Morgan Jones and Wyn Jones. The credit balance on May 16, 1956, was £739 5*s.* 1*d.*
5. Crighton Bramwell and Sir Henry S. Souttar were elected and acclaimed as *Honorary Members* of the Society.
6. Sir Alan Drury was elected an *Extra-Ordinary Member* of the Society.
7. Dr. Max Holzmann was elected a *Corresponding Member* of the Society.
8. The following Associate Members were elected as *Ordinary Members.*

   R. S. Benson
   J. Gibson Graham
   D. Lewes
   R. M. Marquis
   E. Lawson McDonald
   J. F. Pantridge
   D. S. Short
   W. Whitaker
   M. Zoob

9. The following Surgical Members were elected:

   C. Drew
   R. Milnes Walker
   W. F. Nicholson
   G. H. Wooler
   I. M. Hill

10. The following *Associate Members* were re-elected for a further period of three years:

    C. D. Anderson (Glasgow)
    D. H. Makinson (Llandudno)
    H. J. Wade (Manchester)
    A. G. W. Whitfield (Birmingham)

11. The following new *Associate Members* were elected and introduced to the President and the Chairman:

    J. D. Aitchison (Aberdeen)
    E. Besterman (London)
    J. M. Bishop (Birmingham)
    H. R. L. Fraser (Edinburgh)
    R. V. Gibson (London)
    I. R. Gray (Coventry)
    A. Hollman (London)
    J. M. S. Knott (London)
    K. G. Lowe (Dundee)
    R. K. MacCuish (Durham)
    J. T. Shepherd (Belfast)
    R. E. Steen (Dublin)
    R. M. Thomson (Glasgow)
    D. Weitzman (London)

12. Curtis Bain and William Evans were elected Members of the Council in place of Morgan Jones and Wyn Jones (term of office expired).
13. It was agreed that Rule 4 of the Society should be altered to read as follows:

    "There shall be a President of the Society who shall be nominated by the Council and elected by the Society. Nomination of the President by the Council shall be by written ballot, and if no nominee has a two-thirds majority the ballot shall be taken again between the two nominees receiving the most votes. If need be, the President shall have a casting vote. The Council shall give the Society at

least one month's notice of the nomination, and if during that time any other nominations, which must be signed by ten members, are received by the Council then the election shall be by ballot. He shall be elected for two years and may be eligible for re-election for further periods of one year to a total of five years on the recommendation of the Council. He shall be *ex officio* a member of the Council. He will represent the Society at home and abroad and may preside over meetings of the Council but not at the Scientific Meeting of the Society for which a local Chairman will be elected annually."

It was also agreed that Rule 7 should be altered to read as follows:

"Ordinary and Associate Members shall not exceed 225 in number. This includes up to 25 Ordinary Members or Associate Members who may be elected for their interest in cardiovascular surgery."

14. The Secretary announced that in commemoration of the Tercentenary of the death of William Harvey, the Harveian Society of London proposed to hold an International Scientific Congress at the Royal College of Surgeons, London, from June 3 to 7, 1957. Details have not yet been finally decided but the Council of the British Cardiac Society have offered to provide one of the scientific sessions at this Congress.

Scientific Communications

Hæmodynamic and Ventilatory Studies in Mitral Stenosis before and Two Years after Mitral Valvotomy

By K. W. Donald, J. M. Bishop, P. N. Wormald (*introduced*), and O. L. Wade. Twenty-eight patients who had been catheterized before a satisfactory mitral valvotomy were studied 17–51 months after operation (mean 26 months). Good results, as judged clinically, were obtained in 25 of these patients. Striking changes towards normal hæmodynamic behaviour were found. The "P.C.P." pressures were considerably reduced in most patients at rest, but still reached highly abnormal levels on exercise even in patients denying any disability. Resting pulmonary arterial pressures were reduced in all patients but very few approached normal figures. Exercising pulmonary arterial pressures were less than before operation but were still highly abnormal. The pulmonary vascular resistance was considerably reduced particularly in those patients with excellent clinical results.

The cardiac output was, surprisingly, somewhat reduced at rest as compared with the pre-operative study but a number of patients showed a greater increase of cardiac output on exercise than before, although in only one case did it return to the level normal for exercise.

Both resting and exercise ventilations were greatly reduced, in the majority of cases to normal levels.

Intermediate studies 6–12 months after operation provided no evidence of further objective improvement, as judged by these measurements, after this period.

A Pyhsiological Classification of Pulmonary Hypertension with Observations on the Effects of Selective Pulmonary Vasodilatation

By Paul Wood. Pulmonary hypertension in mitral stenosis may be passive, vasoconstrictive, or obstructive.

Passive pulmonary hypertension merely reflects the rise in left atrial pressure, and rarely exceeds 60/30 mm. Hg at rest; these cases usually suffer from symptoms related to the high pulmonary venous pressure, e.g. cough, breathlessness, hæmoptysis, pulmonary œdema, paroxysmal cardiac dyspnœa, and orthopnœa.

Vasoconstrictive pulmonary hypertension complicates 25 to 30 per cent of cases of critical mitral stenosis, the pulmonary vascular resistance being extreme (over 10 units) in half of them. The lack of pulmonary congestive symptoms in this group led to the idea that the high resistance protected the pulmonary venous system from developing dangerously high pressures.

Obstructive pulmonary hypertension is a late complication of mitral stenosis, and is due to secondary occlusive changes in the pulmonary circulation, such as reactive intimal thickening of the small pulmonary arteries and arterioles with or without thrombosis, and recurrent or massive pulmonary embolism.

The view that active vasoconstrictive pulmonary hypertension is in any sense protective has been challenged, and the hypotensive effect of hexamethonium on both the pulmonary arterial and pulmonary venous pressures has been cited as evidence to the contrary. But hexamethonium tends to lower the cardiac output and reduces venous tone, and is therefore an unsatisfactory agent for testing the thesis. To probe the matter further acetylcholine was injected into the pulmonary artery in the belief that a critical dose would have a selective vasodilator action on the pulmonary arterioles in view of the rapidity with which it is inactivated.

The critical dose averaged 1·5 mg. The pulmonary arterial pressure and resistance fell immediately, while simultaneously the left atrial pressure, cardiac output, and systemic blood pressure rose. These results confirm that a high pulmonary vascular resistance is protective in the sense previously defined.

The Hæmodynamic Findings at Thoracotomy in Fifty Cases of Mitral Valve Disease

By W. P. Cleland, Robert E. Rockney (*introduced*), and Max Zoob. Pressure pulses have been recorded at thoracotomy from the left atrium, left ventricle, and pulmonary artery in fifty patients with mitral valve disease. The pressure gradient across the mitral valve was measured and a value for "Ry/v" (Owen, S. G., and Wood, P. (1955), *Brit. Heart J.*, **17**, 41) and Allison's formula (Allison, P. R., and Linden, R. J., 1955, *Lancet*, **1**, 9) was calculated. The findings were correlated with the surgeon's estimate of valve size and the presence or absence of incompetence.

The values for Ry/v were found to be consistently lower in patients with a greater degree of obstruction. The mean value for Allison's formula tended to be lower in patients with pure stenosis and sinus rhythm but there was much individual variation. Regarding the left atrial pulse contour a large *v* wave was usual in mitral incompetence but no absolutely diagnostic pattern could be established.

Left atrial and pulmonary artery pressures and atrioventricular gradients were higher in patients with smaller valve orifices. In patients with comparable valve sizes left atrial pressures were higher in those with sinus rhythm than in those with auricular fibrillation.

Following valvotomy the average left atrial mean pressures were lower, and the fall in pressure was greater in cases in which a larger split was produced. The pulmonary artery pressure fell following valvotomy in a proportion of cases. It fell most often and to a greater extent in patients with high initial pressures. Left atrial pressures and atrio-ventricular gradients showed greater falls in patients with high initial pulmonary artery pressures.

The Pulmonary Arterial Bed in Pulmonary Hypertension: an Arteriographic Study

By David Short. While it is generally agreed that the pulmonary arterial bed is restricted in serious pulmonary hypertension, the nature of this restriction is widely disputed. Some hold that it is due mainly to structural changes in the arteries (or arterioles), others that it is chiefly functional. The problem is one that has an important bearing both on prognosis and on treatment. A technique of post-mortem pulmonary arteriography has been devised which affords a means of determining the extent to which the arterial bed is reduced by purely structural factors. This investigation has been performed on 54 lungs from patients with mitral stenosis, emphysema, congenital heart disease, recurrent pulmonary embolism, lone (or primary) pulmonary hypertension, and diseases unrelated to the cardiovascular and pulmonary systems. In approximately half the cases, there had been severe pulmonary hypertension during life.

The arteriogram showed considerable or great reduction in the arterial bed in every case of severe pulmonary hypertension, and abnormal inter-pulmonary and broncho-pulmonary arterial anastomosis in most of them.

Structural changes in the arteries are an important factor in pulmonary hypertension. They account for its serious prognosis, and militate against successful treatment.

Dye Dilution Curves in the Study of the Hæmodynamics of Mitral Incompetence

By John Shillingford. Dye dilution curves have been used in the study of regurgitant flow through the mitral valve in a series of patients with predominant mitral incompetence. Although no attempt has been made at this time to assess critically the value of this technique for determining the anatomy of the mitral valve before operation, examples of its use in representative patients are given and compared with the clinical and hæmodynamic findings.

The observations have also shown that, although the ratio of forward flow through the aortic valve to regurgitant flow through the mitral orifice in a given patient may vary from minute to minute, the total left ventricular output varies within smaller limits. Lowering the aortic peripheral resistance increases the forward flow and decreases the backflow. This is seen in the effect of exercise in patients with mitral incompetence in whom, although the forward cardiac output rises, the regurgitant flow becomes less. This phenomenon may explain the good exercise tolerance in these patients and the comparatively poor response to treatment once the heart begins to fail.

Extra-Corporeal Circulation (Pump-Oxygenator System of Lillehei-Dewall) and Heart Surgery

By R. Heim de Balsac and (*introduced*) Ch. Dubost, C. Lenfant, J. Guery, J. Passelecq, and M. Weiss. The pump oxygenator system of Lillehei-Dewall appears to the authors to be now the best and the most simple procedure to secure an extra-corporeal circulation during an operation such as opening the heart chambers.

The authors present in a short film this set-up which they improved by increasing the flow and by recovering the blood from the heart.

The first applications to human surgery are gratifying as far as the work of the pump oxygenator system is concerned. But the intracardiac surgical techniques involve often difficult problems.

Left Atrial Size in Patients without Mitral Disease

By W. B. Cobbs (*introduced*) and R. E. Steiner. In a series of 100 patients with hypertension and without clinical evidence of mitral valve disease, left atrial enlargement was observed radiologically in 10 per cent. Autopsy studies of left atrial size by a technique of volume measurement at standardized pressures, has defined the normal distribution of left atrial size measured under these conditions. This varies between 70 and 120 ml.

Patients who in life had congestive heart failure from hypertension, ischæmic heart disease, or aortic valvular disease, frequently showed enlargement of the left atrium when studied radiologically and subsequently post-mortem. The post-mortem findings indicate that the left atrium in the patients mentioned above may be as large as that in some patients with mitral heart disease. Radiological evidence of left atrial enlargement may therefore be misleading in the diagnosis of mitral valve disease when other cardiac lesions are present concomitantly.

The Prognosis of Coarctation of the Aorta

By Maurice Campbell and J. H. Baylis. Published in full: *British Heart J.*, **18**, 475.

Observer Variation in Reports on Electrocardiograms

By L. G. Davies. One hundred electrocardiograms were used to test observer variation, 50 having been reported routinely as indicating infarction, 25 as normal, and the remainder as showing various abnormalities other than infarction. Nine experienced and, for comparison, one inexperienced observer then reported on these, being given the choice of reporting them either normal, abnormal, or showing infarction. Some weeks later the observers read the tracings again.

Disagreement between the observers was found in all three categories. Although there was general or majority agreement on four out of every five tracings, the fifth gave rise to considerable dispute. This disagreement appeared to be due to differences in interpretation and not to errors of observation. There was as much difficulty in deciding between normal and abnormal as between abnormal and infarction.

Each observer's working definition varied, for after the second reading all were found to have changed their opinions in a proportion of the tracings.

The causes of this variation and of disagreement generally have been studied. Certain leads and patterns were particularly controversial, and when these are involved, the diagnostic value of the single electrocardiogram may be much less than is generally realized.

The Arterial Pressure and Pulse with Aortic Stenosis

Lawson McDonald, John Shanks (*introduced*), and William Smith (*introduced*). Normal subjects and patients with aortic stenosis and with hypertension have been studied. The severity of the aortic stenosis was first judged by symptoms; asymptomatic cases were included, also patients with slight and severe symptoms, some of whom underwent aortic valvotomy. The intra-arterial pulse and pressure were recorded, systolic upstroke and brachial arterial mean pressure were measured, and normal values were determined. Prolongation of the upstroke in aortic stenosis was related to severity and in cases with symptoms it was always prolonged beyond a critical length. Although occasionally patients were asymptomatic at this length, the systolic upstroke was usually much shorter in those without symptoms. The brachial arterial mean pressure tended to be above normal in the early and intermediate stages of the disease, but later it fell below normal levels. The value of considering the systolic upstroke in relation to the brachial arterial mean pressure is shown; such data agreed well not only with clinical findings reflecting the severity of the aortic stenosis, but also with electrocardiographic changes. The systolic upstroke was prolonged in hypertension, but it shortened as the heart rate increased. The effect of pulse pressure was insignificant, and of myocardial failure inconstant.

The Effect of Long- and Short-Term Anticoagulant Therapy on the Prognosis of Myocardial Infarction

By M. M. Suzman, *Johannesburg*. The prophylactic value of prolonged continuous anticoagulant therapy in survivors of acute myocardial infarction was tested by comparing the prognosis of groups of (1) 150 patients receiving anticoagulants continuously, (2) 64 patients who discontinued long-term therapy, and (3) 498 patients whose treatment with anticoagulants was limited to the acute phase of the infarction. The prognosis was judged on the basis of the overall and annual mortality rates and of the incidence of subsequent attacks of myocardial infarction.

Drawn from unselected hospital admissions and private practice, the patients were followed after recovery from the presenting acute attack until their death or for periods ranging from 12 to 106 months. Living patients observed for less than one year were excluded.

The total mortality rate was substantially lower (17%) in the patients on prolonged continuous anticoagulant therapy than in those who discontinued their long-term treatment (25%) or received only short-term therapy (43%).

The Mechanism of the Bisferiens Pulse

By P. R. Fleming (*introduced*). Left ventricular and aortic pressure pulses recorded at aortic valvotomy have been superimposed and the gradient across the valve has been measured at regular intervals during systole. The curve representing the changing gradient is used to represent the changing flow rate through the aortic orifice as the two are directly related.

The maximum flow is seen to coincide in time with the aortic anacrotic notch which, it is suggested, is due to the negative pressure exerted alongside the high-velocity stream of blood (Venturi effect). In severe aortic stenosis, the peak aortic pressure is delayed in relation to the maximum flow and the anacrotic notch is therefore situated low down on the upstroke of the pressure pulse. In milder cases, or after a successful valvotomy, the peak aortic pressure is reached earlier and nearer in time to the maximum flow; the anacrotic notch is therefore higher on the upstroke and in even milder cases, when the velocity of flow approaches normal, is not seen at all.

If, however, in a mild case of aortic stenosis, the flow velocity is increased by a large stroke volume, the notch appears on or near the summit of the aortic pressure pulse and is deep (due to the high flow velocity). This is the classical bisferiens pulse of combined aortic stenosis and regurgitation in which the stenosis is relatively mild and the stroke volume very large. The presence of the bisferiens pulse is, therefore, a clear contraindication to aortic valvotomy.

Transposition of the Pulmonary Artery and Aorta with Pulmonary Stenosis

By W. P. Cleland and J. F. Goodwin. Eight patients with transposition of the pulmonary artery and aorta associated with pulmonary stenosis have been studied. The ages ranged from 11 months to 8 years. They were undersized, severely dyspnœic, and extremely cyanosed. The right ventricle was enlarged clinically, radiologically, and cardiographically in all, and seven had a systolic murmur maximum at the left parasternal area. The second heart sound was loud and single in 7 patients. In several the peripheral arterial pulses were of unusually full volume.

In all of them the lungs were oligæmic on X-ray, and the pulmonary arteries were poorly visualized. The heart size and shape varied considerably from case to case.

Angiocardiography showed the aorta arising from the right ventricle, and in 4 of the 5 in whom it was performed, the main pulmonary artery was not opacified. The diagnosis was confirmed at thoracotomy or autopsy in all.

A subclavian-pulmonary anastomosis was carried out in seven, and an aorto-pulmonary anastomosis in one. Three patients died at, or soon after operation, but the remaining 5 were strikingly improved. It is concluded that the diagnosis can be suspected clinically, and usually confirmed by angiocaridography. The differential diagnosis and indications for operation are discussed.

The Pathological Effects of Argentaffin Carcinoma on the Heart

By Reginald Hudson. The primary tumour and its metastases in the liver produce an excessive amount of 5-hydroxytryptamine (serotonin) which circulates in venous blood as far as the lungs, where it is largely removed by the enzyme mono-amine oxidase, and thereafter excreted as 5-hydroxy-indole-acetic acid in the urine.

The major lesions associated with this excess of circulating serotonin are therefore confined to the right heart, causing fibrosis and stenosis of the tricuspid and pulmonary valves. The effects on the tricuspid valve resemble closely those of chronic rheumatism.

In the case to be presented, there were, in addition to the tricuspid and pulmonary valve lesions, metastases in the lungs and these are thought to be associated with minor changes found in the mitral and aortic valves.

The interest of the condition lies in the fact that it is the first time that a " hormone " has been shown to be associated with valvular lesions of the heart, and this leads to speculation as to whether the study of *arterial* blood might reveal some substance, possibly produced in the lungs and removed by the liver, in association with the lesions of rheumatism.

Præcordial Ballistocardiography

By Patrick Mounsey. Palpation of the heart beat yields important information in heart disease and a method was therefore sought to record this movement. An instrument capable of responding to total movements of the chest wall in space was needed, and an accelerometer was therefore chosen, which was

designed and kindly given by Dr. Elliott (Elliott, R. V., Packard, R. G., and Kyrazis, D. T., 1954, *Circulation*, **9**, 281). The accelerometer was attached to the præcordium in selected areas, and records were obtained on a two-channel recorder, using an electrocardiogram or phonocardiogram as a reference tracing.

Præcordial ballistocardiograms have been studied in 20 normal subjects and found to give information about the sequence and direction of forces acting during the cardiac cycle. A study has also been made of the præcordial ballistocardiogram in examples of different diseases, including systemic and pulmonary hypertension, mitral, aortic, and tricuspid valve disease, and left heart failure.

The conclusion was reached that the præcordial ballistocardiogram contributes to our knowledge of cardiovascular dynamics in health and disease, enables us to relate dynamic events to other cardiac phenomena, such as heart sounds, depicts graphically information about the forces responsible for præcordial pulsations, and lastly offers the possibility of an ancillary diagnostic aid in distinguishing between dominant stenosis and incompetence in valvular disease of the heart.

The Ballistocardiogram Before and After Mitral Valvotomy

By C. B. Henderson. Ballistocardiograms were recorded before mitral valvotomy and again three weeks and eight to twelve months after operation in fifty patients with mitral stenosis. The heart rhythm was normal in 38 and auricular fibrillation in 12 patients. In all, cardiac catheterization was performed before valvotomy and in twenty was repeated eight to twelve months afterwards.

Before operation the grades of abnormality of the ballistocardiogram correlated well with the levels of the mean pulmonary artery pressure. Eight to twelve months after valvotomy the ballistocardiograms showed improvement in 32 (64%), no change in 12 (24%), and deterioration in six patients (12%). In the 20 recatheterized after operation an improved ballistocardiogram was accompanied by a fall in the mean pulmonary artery pressure, an unchanged one by a virtually unchanged pressure, and a deteriorated one by a rise in the pressure.

It is suggested that the ballistocardiogram provides useful information both in the selection of patients for mitral valvotomy and in the assessment of the results.

The Nephrotic Syndrome and Mercurial Diuretics

By I. Beswick (*introduced*), F. Gardner, and M. Riddle (*introduced*). The long-term use of mercurial diuretics appears sometimes to have precipitated the nephrotic syndrome. Five cases have been described with convincing pathological and histological changes, but two of these were known diabetics and the kidneys showed diabetic intercapillary glomerularsclerosis in addition to the tubular changes ascribed to mercurials.

In this paper four new cases of the syndrome are described, including the histological findings in the three who died. Reasons for attributing the renal damage to mercurial diuretics are given, and some of the possible factors concerned in the occurrence of the syndrome are discussed.

Three of our cases had received an oral mercurial preparation (chlormerodrin) during the last few months of treatment. The possibility of an increased danger of toxicity with this route of administration is considered. Prophylaxis and treatment of the condition are briefly discussed.

ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

The Direct-vision Intracardiac Correction of Congenital Anomalies by Controlled Cross Circulation. Results in Thirty-two Patients with Ventricular Septal defects, Tetralogy of Fallot, and Atrioventricularis Communis Defects. C. W. LILLEHEI, M. COHEN, H. E. WARDEN, and R. L. VARCO. *Surgery*, **38**, 11–29, 1955.

The use of controlled cross-circulation methods has enabled operations to be performed under direct vision on the interior of the heart in 32 cases since March, 1954, at the University of Minnesota Hospitals.

The authors calculate that if the patient's heart is to be excluded for any period of time from the circulation, a volume of blood varying between 25 and 40 ml. per kg. body weight per minute has to be circulated, which is considerably less than has previously been thought to be necessary. The principle of the cross-circulation technique employed is to take blood from the descending aorta of a donor through a catheter introduced through the femoral artery and to pass this by means of a pump into the base of the patient's aorta. The return flow from the patient is obtained from both venæ cavaæ through catheters inserted through stab wounds in the right atrium; the blood is led to a venous reservoir with an air trap and returned via a second pump to the femoral vein of the donor.

The use of the cross-circulation technique has so far been confined to the surgical correction of congenital abnormalities. Of 22 cases of interventricular septal defect treated, the operation was successful in 15. Of the 7 deaths, 6 occurred in infants under 2 years of age. Six cases of the tetralogy of Fallot have been treated, the stenosis being resected and the ventricular defect being closed at the same time; 3 of these patients survived. Four patients with other congenital defects have also been operated on, 2 surviving. The patients were all grossly incapacitated at the time of operation, which would not have been considered a practical proposition without the cross-circulation technique. The donors suffered no ill-effects except in 2 cases—one in which severe hypotension developed and required cardiac massage, and another in which air embolism produced transient neurological sequelæ.

[This communication is one of the most important contributions yet made to cardiac surgery and should be read in detail by anyone interested in the subject. The question will be raised as to how far and to what extent donors can be used without exposure to risk, but that will be a problem for the individual surgeon.]

T. Holmes Sellors

Cardiac Diagnosis. A Physiologic Approach. ROBERT F. RUSHMER, M.D. Pp. viii and 447. W. B. Saunders Company, London. Price 80*s*. 6*d*.

The widespread use of instrumental techniques in the study of the circulatory changes in heart disease has led to the production of several recent books from American authors on the physiological approach to cardiology. In the present work nearly three-quarters is devoted to basic physiology and there are excellent and critical accounts of the information which may be obtained with these special methods of investigation, with an unusually complete bibliography. The shorter clinical section is much less satisfactory and gives an inadequate account of clinical diagnosis and of the information that can be obtained by clinical examination of the patient. Differential diagnosis is hardly discussed at all and the clinical aspects of hypertension are discussed in less than a page. Although this book cannot be recommended as a practical manual of cardiac diagnosis it does provide one of the best recent accounts of the applied physiology of the circulation.

Graham Hayward

Myokardstoffwechsel und Herztherapie. VON DR. FR. PENDL, Heidenheim/Brenz. 1954. XII, 248 Seiten, 52 Abbildungen, Ganzleinen DM 29.70. GEORG THIEME VERLAG.

This book, entitled Myocardial Metabolism and Cardiac Therapy, aims at linking up what is known about the metabolism of the muscle fibre of the heart, normal and deranged, and some scheme of therapy which will restore the function to health. This is an excellent idea. The first part describes the structure of the cell, as revealed by the most modern techniques; then comes a description of the sources of the cardiac energy. The function of the phosphorus compounds is considered in detail. Then follows a chapter on the influence of the mineral substances such as potassium and calcium. An interesting chapter discusses the pathogenesis of œdema, and another considers protein metabolism and defects in the liver. Sugar metabolism is fully dealt with. This is a thoughtful book and treats an important subject from a modern point of view. The diagrams and print are good. Each section has a complete and useful summary.

Terence East

Levarterenol Bitartrate (Levophed) in the Treatment of Cardiac Arrhythmias. J. T. MCGINN and J. SCHLUGER. *Amer. Heart J.*, **50**, 625–633, 1955.

The authors report 6 cases in which supraventricular tachycardia was relieved by the administration of L-noradrenaline given intravenously at the rate of 20 to 40 drops per minute of a solution containing 8 to 18 mg. of noradrenaline per litre. The effect of the drug is to increase blood pressure; it is assumed that by this means the vagus nerve is reflexly stimulated and thus causes cardiac slowing. In one case of auricular flutter there was a temporary slowing of the heart rate, but the abnormal rhythm persisted.

H. E. Holling

Precipitation of Ventricular Arrhythmias due to Digitalis by Carbohydrate Administration. E. PAGE. *Amer. J. Med.*, **19**, 169, 1955.

Potassium depletion has been shown to predispose to the development of cardiac manifestations of digitalis intoxication and to enhance cardiac arrhythmia when already present. As electrocardiographic changes resembling those of potassium deficiency may occur after meals (and are thought to be due to dietary carbohydrate) the author has investigated the possibility of a relationship between carbohydrate metabolism and clinical digitalis intoxication.

At Birmingham, Alabama, 37 patients receiving digitalis in various dosages were studied in the fasting state, serial electrocardiograms being taken before and after giving a dose of 100 g. of glucose by mouth. Ventricular arrhythmias were precipitated by this procedure on 15 occasions in 7 cases, which are described in some detail.

The clinical implications of these findings, which the author attributes to a reduction in the serum potassium level, are discussed. The possibility that serious arrhythmias may be precipitated in digitalized patients by the administration of carbohydrate is of some importance, especially in cases of vomiting resulting from overdosage of digitalis, in which infusions of glucose solution may be the chief means of sustaining adequate nutrition, and in patients with recent myocardial infarction.

Francis Page

Relaxants and the Human Cardiovascular System. M. JOHNSTONE. *Anaesthesia*, **10**, 122, 1955.

To study the effect of relaxant drugs on the cardiovascular system electrocardiograms were obtained during anæsthesia in a number of cases at the Royal Infirmary, Manchester. It was found that normal doses of curare had no significant atropine-like effect on the partly inhibited heart. Gallamine, on the contrary, invariably exerted a strong atropine-like effect in these circumstances, and in the presence of carbon dioxide retention caused ventricular arrhythmia. Suxamethonium sometimes gave rise to transient cardiac depression—presumably by a muscarinic effect similar to that of acetylcholine—and 4 cases of cardiac collapse are cited. In 30 per cent of cases after suxamethonium there was flattening of the T wave associated with depression of the S–T segment. There were no changes in the electrocardiogram when laudexium methylsulphate was given.

The electrocardiographic response to intubation under various relaxants was also studied in 75 patients. No significant changes were noted with suxamethonium, but with gallamine there were laryngeal reactions accompanied by a sharp increase in the heart rate and, in some instances, by ventricular extrasystoles. All patients given curare had tachycardia on intubation, and in 28 per cent there were ventricular extrasystoles which disappeared with the return of efficient respiratory exchange.

It is pointed out that the adrenergic effect on the heart of ether, chloroform, and cyclopropane may be dangerously augmented by retention of carbon dioxide. Gallamine, by its vagolytic action, may further increase the sympathetic preponderance, and then ventricular arrhythmia is likely. *Ronald Woolmer*

Phlebitis. A Study of 748 Cases at the Boston City Hospital. J. J. BYRNE. *New Engl. J. Med.*, **253**, 579–586, 1955.

The natural history of phlebitis and the prophylactic value of vein ligation in this condition were studied in 748 cases admitted during the last 10 years to the Boston City Hospital, the investigation being confined to those cases in which there were signs of deep phlebitis in the legs.

The incidence of phlebitis was highest in the age group 50 to 79 years; 83 per cent of the cases occurred in patients over 40. Cardiac disease was the commonest pre-disposing factor (28% of cases), followed by post-operative phlebitis (23%), and trauma (11%). In 49 patients (6%) there appeared to be no predisposing cause. The remaining cases were associated with sepsis, varicose veins, hemiplegia, pregnancy and labour, or cancer. The author noted, as others have done, that mortality from pulmonary embolism was highest in patients with the fewest clinical signs and symptoms in the legs.

Conservative treatment was given to 345 patients, 128 (37%) of whom died; 369 received surgical treatment (ligation of the vena cava in 7 and bilateral division of the femoral vein in the remainder), of whom 8 (21%) died. In 8 of the cases treated surgically anticoagulant therapy had been given and embolism had occurred before operation. Of 32 patients given anticoagulant therapy, 9 died (5 from pulmonary embolism), although the dosage of the anticoagulant was apparently adequate.

The author points out that while an exact comparison was not possible it did appear that the patients treated surgically fared better than those treated conservatively. Discussing the relation between premonitory pulmonary embolism and mortality he states that the first attack was fatal in 122 out of 144 cases of fatal pulmonary embolism in patients with pre-existing phlebitis—that is, only 22 patients had a warning attack. The post-phlebitic syndrome developed within 1 to 5 years in 31 out of 67 patients treated surgically, and in 34 out of 39 treated conservatively. *F. B. Cockett*

The Roentgen Appearance of the Pulmonary Veins in Heart Disease. H. L. STEINBACH, T. E. KEATS, and G. E. SHELINE. *Radiology*, **65**, 157–168, 1955.

In the postero-anterior radiographs of the chest the veins of the right lower lobe and, less frequently, those of the right upper lobe and left lower lobe can be distinguished. The lateral view shows the superimposed shadows of both lower-lobe veins converging towards the posterior aspect of the left atrium. In the left anterior oblique view the main venous trunks of the right lung are superimposed on the heart below and slightly posterior to the pulmonary artery. The smaller venous branches from the lung converge towards the main trunks like the spokes of a wheel.

It is of great importance to assess the degree of vascu-

larization of the lungs in the diagnosis of heart disease. The authors therefore made an attempt to evaluate separately the pulmonary arteries and veins. In pulmonary stenosis they have found that, although the main pulmonary artery is dilated and the hilar branches may appear normal, the pulmonary veins are smaller than normal. In one instance in which a clinical diagnosis of pulmonary stenosis was made large pulmonary veins were found, and catheterization showed that the stenosis was complicated by a patent ductus and by an anomalous pulmonary vein entering the right atrium. The demonstration of small pulmonary veins has also been helpful in cases of Fallot's tetralogy, tricuspid atresia, and truncus arteriosus. Enlargement of the veins was found in many instances of left-to-right shunt. In a survey of 100 proved cases of patent ductus arteriosus visible enlargement of the pulmonary veins was observed in 71.

In acquired mitral valve disease with pulmonary hypertension the pulmonary veins in general appear normal. This, it is considered, is due to the narrowing of the peripheral pulmonary arteries which has been shown to occur in pulmonary hypertension secondary to mitral stenosis.

Kenneth A. Rowley

The Effect of Oral 1-Hydrazinophthalazine Therapy on Renal Function in Essential Vascular Hypertension. I. J. MADER and L. T. ISERI. *Amer. Heart J.*, **50,** 556, 1955.

At Detroit Receiving Hospital (Wayne University), Detroit, 14 patients with severe hypertension were treated with oral 1-hydrazinophthalazine (" apresoline ") and subcutaneous hexamethonium. From initial doses of 25 mg. and 3 to 5 mg. respectively the dosage was gradually increased to a maximum ranging from 400 to 900 mg. of 1-hydrazinophthalazine and from 20 to 100 mg. of hexamethonium daily. The patients were observed in hospital under controlled conditions, blood pressure being recorded twice daily. Immediately before starting therapy and again 14 to 41 days afterwards the renal clearances of inulin and PAH were measured and from the results the glomerular filtration rate, renal plasma flow, and maximum tubular excretory capacity were calculated. In some cases the cardiac output was measured by cardiac catheterization. In 12 of the patients there was a fall of blood pressure greater than 15 mm. Hg, and in 10 of these the renal studies showed that a decrease in the afferent arteriolar resistance had occurred and that renal plasma flow had increased, although no significant change in cardiac output was observed, indicating a decrease in the renal ischæmia. The duration of the effect is not known. *H. E. Holling*

Mitral Valvotomy: A Follow-up of 45 Patients for Three Years and over. C. BAKER, R. BROCK, and M. CAMPBELL. *Brit. med. J.*, **2,** 983, 1955

In a detailed and careful study of 45 patients followed up for 3 years or more after operation for mitral stenosis at Guy's Hospital, London, the authors analyse the various factors which may influence the results, and attempt to answer the question whether the effects of mitral valvotomy are lasting or not.

At the end of one year the result was considered good in 38 cases, but after 3 years the figure was only 27. Thus the condition of 11 patients had deteriorated during this period, and possibly a smaller proportion will continue to relapse as the years progress. The size of the opening obtained at operation appeared to bear a close relation to the long-term result. If there was regurgitation or an opening of only 2 cm. diameter at the end of the operation the results were poor, while with an opening over 3 cm. in diameter the long-term results were much more satisfactory. Regurgitation did not necessarily preclude lasting benefit, except when associated with calcification of the valve. The size of the heart, the presence or absence of auricular fibrillation, and the degree of disability before operation had little influence on prognosis: in fact most patients with auricular fibrillation did well. On the other hand fibrillation that developed after the operation and could not be controlled was an unfavourable feature. Pulmonary hypertension was invariably reduced by valvotomy, and the greater the degree of hypertension present originally, the greater was the degree of improvement after operation. In young patients the risk of recrudescence of rheumatic activity causing re-stenosis is difficult to assess; there was evidence of such re-stenosis in 3 of the authors' cases.

The authors conclude that in a proportion of cases the original benefit of the operation will be lost as years go by, but that this proportion is likely to be small in comparison with the more lasting benefit obtained by the majority.

T. Holmes Sellors

An Analysis of Fifty Patients Treated by Mitral Commissurotomy Five or More Years Ago. R. P. GLOVER, T. J. E. O'NEILL, and O. H. JANTON. *J. thorac. Surg.*, **30,** 436–451, 1955.

The first 50 consecutive patients undergoing mitral commissurotomy approximately 5 to 6 years ago have been subjected to a detailed analysis in an attempt to ascertain their present subjective and objective status. There was an operative mortality of 6 per cent (3 patients) and subsequent death, 6 weeks to 3 years later, occurred in 12 per cent (6 patients). The remaining 41 patients (82%) are living and these have formed the basis for the following conclusions.

30 patients (73% of those living or 60% of the original 50) are in better condition and living a more nearly normal life than they were prior to surgery. According to the patients' and their family physicians' own appraisal of the present clinical status of these 41 living patients, 36 (88% of those living, or 72% of the original 50) are better after 5 years than they were prior to surgery. If one were to judge the present clinical status of these patients on the basis of their murmurs alone, it would be impossible to come to any definite conclusions. Only 4 of these 41 living patients have a heart free of murmurs. Eleven have lost all evidence of their original mitral diastolic murmur. Fourteen patients now have a mitral systolic murmur of varying degrees which was not present prior to surgery. Those patients who have a pure murmur of

mitral stenosis indicative of a small mitral orifice obtain the best results from mitral commissurotomy.

Although the electrocardiographic changes following surgery do not always show conclusive evidence of improvement, they often indicate some return towards the normal. 10 (24%) of the 41 living patients now have a cardiac silhouette that is obviously smaller than it was prior to surgery, 26 (63%) have a cardiac mass which is of the same size as that noted before surgery, and in 5 (13%) the heart size is obviously larger.

In 20 (49%) of these patients valvular calcification was present and the degree of improvement in these, although quite satisfactory was not as great as that seen in the others. Evidence of rheumatic activity was observed during the postoperative period in 8 patients (19·5%). No evidence of valvular restenosis has been observed in the 41 living patients nor in the valves of those who died in the postoperative period.—[Author's summary, abridged.]

The Significance of Previous Embolism for the Prognosis of Commissurotomy for Mitral Stenosis. A. Actis-Dato and F. Morino. *Minerva med.* (*Torino*), **2,** 255–263, 1955.

A review of the histories of 500 cases of mitral stenosis in which commissurotomy was performed at the University Cardiac Surgery Centre, Turin, showed that 52 patients (10%) had experienced embolic episodes preoperatively. At operation embolism was observed in 5 other patients, of whom 3 had died, and subsequently a further 14 patients suffered embolism which proved fatal in 3.

The authors have modified their previous view that operation should be deferred for at least 6 months in the presence of embolism, and now advise early operation in spite of this event, although such patients are at greater risk, embolism occurring in 11·5 per cent of them as against only 3 per cent of the remaining 448 cases, and resulting in a mortality of 6 per cent as against 0·7 per cent. In none of the 49 patients previously experiencing embolism and surviving operation has there been further evidence of this complication.

The authors express the view that with exclusion of the auricle and the improvement in cardiac function the patient is protected against further episodes of this kind.

C. A. Jackson

Surgical Correction of Tetralogy of Fallot. Results in First One Hundred Cases Six to Eight Years after Operation. W. J. Potts, S. Gibson, E. Berman, H. White, and R. A. Miller. *J. Amer. med. Ass.*, **159,** 95–99, 1955.

The authors here give details of the long-term results of aortic-pulmonary anastomosis for Fallot's tetralogy in the first 100 cases so treated at the Children's Hospital, Chicago, since 1946. All the patients were under 16 and 35 were less than 4 years of age. Before operation 60 were classed as "bad-risk cases." The standard Pott's operation was performed in all but one At first a 5-mm. anastomosis was made, but this was soon reduced to 4 mm. except in very young children. A second operation was necessary in 4 cases. The operative mortality was 9 per cent, a disproportionate number of deaths occurring among the youngest patients.

The difficulties in evaluation of the results are stressed. The authors have undertaken a very careful follow-up, and have assessed the patients on clinical grounds. They have demanded a high standard before classifying a result as "good," but despite this they have felt justified in placing 68 per cent in this group, while in 16 per cent the result was classified as "fair." Cardiac enlargement has occurred in many patients, but its extent has not been closely related to the clinical result, and although it has often occurred soon after operation, it has not been progressive. There have been 5 late deaths, only one of which was due to a cardiac cause. *J. R. Belcher*

The Surgical Anatomy of Atrial Septal Defects: Experiences with Repair under Direct Vision. F. J. Lewis, M. Taufic, R. L. Varco, and S. Niazi. *Ann. Surg.*, **142,** 401–417, 1955.

In this paper from the University of Minnesota, Minneapolis, the authors discuss the anatomy and repair of atrial septal defects on the basis of observations made during 35 operations in which the cardiac inflow was occluded during hypothermia. They describe the four types of defect encountered as follows: (1) Foramen ovale defect (23 cases). The valve is often present as a fenestrated membrane, and anomalous venous drainage or mitral stenosis are associated conditions in some cases. Care must be taken to ensure that the closing suture does not divert any vein into the wrong atrium. (2) High defect (5 cases). This lies just below the superior vena cava, separate from the fossa ovalis (which may also be patent), and is always associated with anomalous drainage of a pulmonary vein. (3) Continuous defect (one case). This is a high defect with anomalous drainage, extending inferiorly into a patent foramen ovale—"absent septum." (4) Low defect—part of persistent common atrioventricular canal (6 cases). This may be a persistent ostium primum with notched mitral valve; in repair, which is difficult, injury of the conducting system is likely, leading to heart block; the more serious common atrioventicular canal, or incomplete double heart, with an associated interventricular defect has not been successfully repaired.

Of the 29 patients with defects of the first three types, 3 died; the remainder, the oldest of whom was 52, were improved, the defect being completely closed in all except 2. Ventricular fibrillation occurred in 11 patients, but was reversed in all but one.

[This paper, which includes good illustrations, should be read in full by all who are interested in the subject.]

M. Meredith Brown

The Results of Direct Vision Closure of Ventricular Septal Defects in Eight Patients by Means of Controlled Cross Circulation. C. W. Lillehei, M. Cohen, H. E. Warden, N. R. Ziegler, and R. L. Varco. *Surg. Gynec. Obstet.*, **101,** 446–466, 1955.

In a previous paper (*Surgery*, 1955, **38,** 11; *Abstracts of World Medicine*, 1956, **9,** 123) the authors described the

principle and technique of a method of cross-circulation whereby a patient's heart can be excluded from the circulation and an intracardiac defect repaired under direct vision. In the present article they describe the application of this method in the repair of ventricular septal defects.

The operation consisted in freely opening the myocardium of the right ventricle by an incision parallel to the coronary arteries, the edges of the wound being retracted by stay sutures. The margins of the ventricular defect, which in all 8 cases was high in the septum under the leaflet of the tricuspid valve and close to the aortic leaflet of the mitral and the cusps of the aortic valves, were then defined carefully, this procedure being facilitated by division of the papillary muscles of the tricuspid leaflet and their retraction upwards. Sutures were then applied to close the defect, and the papillary muscles sutured back in their original position. (It is emphasized that before closure is completed the left ventricle must be filled with blood or other fluid to avoid the risk of air embolism.) Closure of the right ventricle was then carried out with a continuous suture.

The period during which the heart and lungs were totally by-passed varied between 5 and 26 minutes. Two of the patients died some days after operation, but both these infants were very ill at the time of the operation. In 4 of the survivors closure of the defect has been confirmed by catheterization. There was no complication involving any of the donors.

[The case-reports provided afford interesting reading.]

T. Holmes Sellors

Reduced Intrathoracic Circulation as an Aid in Angiocardiography. An Experimental Study. I. BOEREMA and J. R. BLICKMAN. *J. thorac. Surg.*, **30**, 129, 1955.

Many of the difficulties still encountered in angiocardiography are considered to be due to rapid dispersal of the contrast medium and the great mobility of the walls of the heart and great vessels during the cardiac cycle. This has necessitated the rapid injection of a concentrated medium and the use of expensive apparatus to obtain serial radiographs by frequent, short exposures. These difficulties could be overcome if the blood flow through the heart were reduced during the examination.

The effect of respiration on the circulation has been discussed by a number of authorities since Valsalva's original observation, notably by Weber who, in 1850, showed that forced expiration when the glottis was closed was followed by immediate cessation of the heart beat with rapid weakening and disappearance of the radial pulse; he concluded that this was due to compression of the venæ cavæ and right atrium. This observation has since been confirmed, and the present authors, at the University of Amsterdam, carried out experiments on animals to determine whether the mechanism described by Weber could safely be utilized in angiography in the human subject. The trachea was intubated with a cuffed tube and a water manometer was placed in the anæsthetic circuit so that exact control of the pressure exerted by manual compression of the bag was possible. A pressure of 30 to 60 cm. of water produced the desired decrease in cardiac output. Direct blood pressure recordings were obtained from different positions under varying conditions. The technique and results of the experiments are described and angiocardiograms are reproduced.

Sydney J. Hinds

Prothrombin Pattern over the 24 Hours in Patients Receiving Oral Anticoagulants. H. L. MATTHEWS, M. J. MEYNELL, C. G. PARSONS, E. G. WARBURTON, and J. A. H. WATERHOUSE. *Brit. med. J.*, **2**, 947–948, 1955.

Of 19 patients with myocardial infarct, coronary insufficiency, venous thrombosis, or pulmonary embolism who were under treatment at the General Hospital, Birmingham, and were already stabilized on oral anticoagulant therapy, 10 were given the required dose of phenindione (" dindevan ") and 9 ethyl biscoumacetate (" tromexan ") at 6 p.m. one evening the prothrombin time being thereafter estimated by Quick's method every 2 hours for the next 24 hours.

The authors found that the prothrombin concentration remained at a relatively high level for 8 to 10 hours and then fell to its lowest level about 18 hours after administration of the anticoagulant. The patients receiving ethyl biscoumacetate tended to show greater variations of the prothrombin concentration during the day than those given phenindione. It is concluded that the blood required for routine estimations of prothrombin time should be withdrawn at the same time each day, and that phenindione and ethyl biscoumacetate are effective in a single daily dose once the patient has been " stabilized."

[It is unfortunate that the results are expressed in the form of prothrombin concentration instead of prothrombin time. The prothrombin concentrations were presumably calculated from dilution curves, and on this basis the apparently dramatic fall in concentration (as, for example, in the graph for ethyl biscoumacetate) represents a difference of only about 4 seconds in the prothrombin time; at this level the experimental error is approximately 2 seconds. The conclusions drawn from these observations are probably valid, but the trends are not as significant as the figures and graphs seem to suggest.]

T. B. Begg

A.B.C. de Cardiologie. P. BARDIN, H. HEIM de BALSAC, G. MAYONADE, and P. STEIN. Pp. 557. *Expansion Scientifique Française*. (No price given.)

The title of this book is misleading as it consists of 37 essays, arranged alphabetically, on various cardiological topics. The subject matter includes the various symptoms of heart disease, special methods of investigation such as radiokymography and vectorcardiography, the effects of obesity on the cardiovascular system, cardiac enlargement in infants, and the assessment of systolic murmurs. There are also chapters on the effect of kyphoscoliosis on the heart, and radiology of the heart. The wide range of subjects covered, many of them not dealt with adequately or at all in the ordinary text books, makes this a useful addition to the books on cardiology.

Graham Hayward

Physiopathology and Diagnosis of Adhesive Pericarditis. Prof. LUIGI CONDORELLI in collaboration with A. TURCHETTI, G. SCHIROSA, A. STRANO, M. SANGIORGI, F. TESTONI, G. FILOCAMO, and A. TEDESCHI. Pp. 273, illustrated. (Price not given.) Milano, Arrigo Recordati, 1954.

Professor Condorelli whose work on venous circulation is well known is well qualified to write an authoritative treatise on constrictive pericarditis. "Concretio" and "accretio" of the pericardium, though more often associated, are being treated separately for in their pure form they give rise to different circulatory effects. Constrictive pericarditis mainly affects the right heart and through it the venous circulation. Contrary to the increased venous pressure in congestive heart failure the syndrome of venous hypertension in constrictive pericarditis is an active process, kept up by an increased tonus of the peripheral veins. Absent or diminished jugular pulsation, absence of respiratory pressure variations, paradoxical behaviour of the venous pressure are the features of right atrial or ventricular constriction. The location of maximal constriction is assessed by venous pressure tracings, intracavitary oscillography, and radiokymography; accretio by introduction of air into the mediastinum which also gives information about the extent of mediastinal involvement. Tomography added to pneumomediastinum produces impressive radiographs which side by side with controls clearly illustrate the topography of maximal adhesions and furnish the surgeon with important data where to operate. A detailed description of the instrumental technique completes this excellent monograph. *C. Papp*

The Heart in Acute Glomerulonephritis. T. R. MURPHY and F. D. MURPHY. *Ann. intern. Med.*, **41**, 510–532, Sept., 1954.

The cardiac changes in acute glomerulonephritis were studied at Milwaukee County Hospital, Wisconsin. In the authors' view cardiac involvement is indicated by the presence of one, or any combination, of the following: (1) clinical heart failure; (2) radiological evidence of enlargement of the heart; and (3) electrocardiographic (ECG) abnormalities. On this basis cardiac changes were found in 41 out of 88 cases of glomerulonephritis. Heart failure, which was present in 22 of the cases, appeared to be more frequent in patients over 21 years of age and in those with moderate or severe hypertension, although hypertension itself was not considered to be the sole cause of failure. Cardiac failure occurred in 9 of 16 patients with convulsions. The most frequently observed abnormalities in the ECG were T-wave changes in lead 1. The authors point out that heart failure may not always be recognized because the œdema of acute nephritis may obscure distension of the neck veins. Further, it may not be suspected since little is known about the incidence of heart failure in acute nephritis. *James W. Brown*

Right Ventricular Block. A Clinical Study of 232 Cases. G. FISCHER, M. M. VASTESAEGER, and P. VANDERSTRAETEN. *Acta clin. belg.*, **9**, 230–261, May–June, 1954.

The authors present, from the Medico-chirurgical Institute, Ixelles, Belgium, a clinical study of 232 cases of right ventricular block, comprising 130 cases from private practice and 102 from three hospitals, 72 per cent of the patients being male and 28 per cent female. In the youngest patients the lesion was of congenital ætiology only and all these patients showed minor (incomplete) degrees of block (QRS complex of 0·10 to 0·12 second). The patients in the age group 20 to 40, almost exclusively male, included 45 per cent of cases of unknown ætiology. By relating these to the figures for proven cases of coronary atherosclerosis the authors contend that this disease is in fact the cause of block in such cases, and occurs at an earlier age in men than in women; in this group, 81 per cent of cases were attributed to coronary disease. Of 40 cases presenting only minor degrees of block—this small proportion is attributed to very strict selection—17 (42%) were due to incontestable coronary arterial disease and 10 (25%) were of unknown ætiology. With increasing age the proportion of cases of minor block diminished.

In discussing the development of block in cases of cor pulmonale and mitral stenosis the authors observe that the majority of these patients are aged over 40 and possibly subject to the additional factor of coronary disease. The authors cite cases of cardiac infarction and coronary sclerosis to support their belief that damage to an area of myocardium without damage to the bundle of His can cause block, whereas considerable interference with the bundle of His may occur without block. The authors suggest that, apart from the factor of infection in acute rheumatism, the sole determinant of right ventricular block is myocardial ischæmia, whether relative (as in ventricular hypertrophy), in which case it leads to a minor degree of block, or absolute, leading to major degrees of block. *R. S. Stevens*

Hypertension and Its Control by Hexamethonium. K. SHIRLEY SMITH, P. B. S. FOWLER, and V. EDMUNDS. *Brit. med. J.*, **2**, 1243–1250, 1954.

The authors report on 83 patients with hypertension who were treated with hexamethonium bromide at Charing Cross Hospital and followed up for periods varying from 6 months to 3 years. The drug was given parenterally to 51 patients and by mouth to 32; in 16 cases of the former group and 7 of the latter either treatment was abandoned or the patient died. Of the remaining 35 patients who received parenteral treatment, a "good" response in terms of reduced blood pressure was noted in 11 and a "fair" response in 12; of the 25 patients on oral treatment the response was "good" in 3 and "fair" in 5. However, many patients experienced relief of such symptoms as headache and angina despite an inadequate reduction in blood pressure.

K. G. Lowe

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